and sulfuric acids upon bromopentamethylbenzene gave 4-bromo-5,6-dinitrohemimellithene, in which two methyl groups had been replaced by nitro groups.

3. The benzyl nitrates V and VI were intermediates in the replacement of methyl groups by nitro groups; this may possibly be the course of other aromatic nitrations in which alkyl groups are replaced by nitro groups.

MINNEAPOLIS, MINNESOTA RECEIVED FEBRUARY 12, 1940

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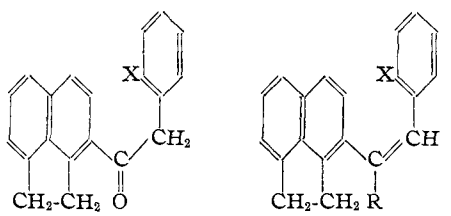
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# 7-Cholanthroic Acid

BY LOUIS F. FIESER AND GLEN W. KILMER[1]

The recently described preparation of 1-acetoacenaphthene by the acetylation of the hydrocarbon in the presence of liquid hydrogen fluoride[2,3] has rendered this ketone far more readily available as an intermediate for synthesis than any other 1-substituted acenaphthene, and the present research was undertaken to determine whether this or other 1-acyl derivative obtainable with the use of hydrogen fluoride could be employed as the starting point for the construction of the cholanthrene ring system.

The ready availability of the 1-aceto compound, which in large scale preparations has now been obtained in yields as high as 45% of the theory, is dependent upon the formation of a large proportion of the 1-isomer and also upon the fact that this is less soluble than the 3-ketone present in the mixture and is very easily separated. This favorable combination of factors has not been encountered in such other hydrogen fluoride acylations as have been investigated,[2a] for in the benzoylation, succinoylation and condensation of the hydrocarbon with crotonic acid by the hydrogen fluoride method, the amount of 1-substitution is small or negligible and no greater than in the Friedel and Crafts reaction. Although the prospects of obtaining other 1-acyl derivatives easily by direct hydrogen fluoride acylation are thus none too great, some trial was made of the condensation with phenylacetic acid derivatives with the thought that ketones of the type I might afford a short synthetic route to cholanthrenes. Thus a derived unsaturated compound (II) might be convertible to a cholanthrene by Pschorr ring closure (X = $NO_2$) or by the alkali fusion method employed by Hewett[4] (X = Br).




I II

In a preliminary trial the hydrogen fluoride acylation of acenaphthene with phenylacetic acid itself was found to give a difficultly separable ketone mixture which on fractional crystallization afforded in 30% yield a pure compound identified as 3-phenylacetoacenaphthene by hypoiodite oxidation to the corresponding acid. The desired 1-isomer (I, X = H), which was similarly characterized as to structure, was isolated with difficulty and in only small amounts through the picrate. *o*-Bromophenylacetic acid, prepared from *o*-bromobenzoic acid by the Arndt–Eistert[5] reaction in 61% over-all yield, behaved similarly and gave a mixture from which two apparently pure compounds were isolated but only by tedious processing and in very small amounts. In view of these unfavorable indications, this approach was abandoned.

We then undertook to prepare intermediates of the type II starting with 1-acetoacenaphthene (III). Two routes were explored for the conversion of this ketone into 1-acenaphthylacetic acid (VII), the first being via the acid chloride and diazo ketone by the Arndt–Eistert procedure.[5] While the over-all yield of 50% is adequate, the process is time-consuming and not well adapted to the preparation of a quantity of the acetic acid derivative. Furthermore, the purified product probably was contaminated with a trace of the more sparingly soluble 1-acenaphthoic acid, for the melting point was not quite as high as that of

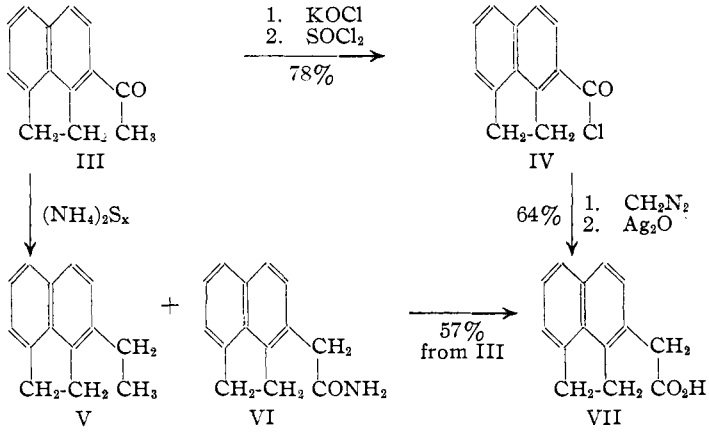
(1) Du Pont Graduate Fellow, 1939–1940.

(2) (a) Fieser and Hershberg, THIS JOURNAL, **61**, 1272 (1939); (b) **62**, 49 (1940).

(3) Fieser and Cason, *ibid.*, **61**, 1740 (1939).

(4) Hewett, *J. Chem. Soc.*, 1286 (1938).

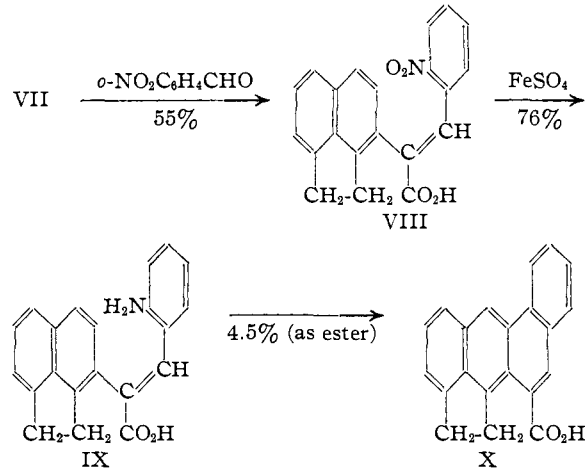
(5) Arndt and Eistert, *Ber.*, **68**, 203 (1935).




material prepared by the Willgerodt reaction,[6] which proved to be generally more satisfactory. This in the simplest case consists in heating a methyl ketone with yellow ammonium sulfide and results in the formation of an amide derivative, $ArCH_2CONH_2$, and in a certain amount of reduction. In a number of small scale experiments conducted in sealed tubes it was found that with 1-acetoacenaphthene the results are improved by the use of added dioxane and by conducting the reaction at a temperature (160°) considerably lower than recommended by Willgerodt. In the best case the yield of slightly colored but sharply melting acid (VII), isolated after hydrolysis of the crude amide, was 57%. This result could not be matched in large scale preparations conducted in an autoclave, for in the best case the yield of 1-acenaphthylacetic acid was 37% and considerable 1-ethylacenaphthene (47%) was produced. In one run in the autoclave the yield of the hydrocarbon was 67% of the theoretical. Cook, Haslewood and Robinson[7] prepared this hydrocarbon in a different way and reported the melting point of a purified sample as 30°. The redistilled material from the Willgerodt reaction had the m. p. 34.8–35.1° (constant) after a single crystallization from methanol.[8]

The Perkin condensation of 1-acenaphthylacetic acid with *o*-chlorobenzaldehyde proceeded satisfactorily (55%) to α-(*o*-chlorobenzal)-1-acenaphthylacetic acid (II, X = Cl, R = $CO_2H$), but fusion of this substance with potassium hydroxide or refluxing with potassium hydroxide in quinoline gave tars from which only traces of starting material could be isolated. Although these experiments were conducted with only rather small quantities of the chloro acid, the results discouraged further attempts to effect cyclization by this route. The case is comparable to an unsuccessful trial in the chrysene series.[9]

The Pschorr reaction then was tried, the intermediate α-(*o*-nitrobenzal)-1-acenaphthylacetic acid (VIII) being obtained by the Perkin condensation and reduced satisfactorily with ferrous sulfate and ammonia. Hydrogenation of the nitro compound in the presence of Adams catalyst




was less successful, for the yield of the amine IX was poorer (53%) and two unidentified neutral products were formed, one in 18% yield. The Pschorr ring closure proceeded poorly under all conditions tried, the procedure eventually adopted consisting in diazotization with isoamyl nitrite and treatment with Gattermann copper. The reaction gave a tarry acidic product which could not be purified as such, but by esterification with diazomethane and purification of the ester by

(6) Willgerodt, *Ber.*, **20**, 2467 (1887); **21**, 535 (1888); *J. prakt. Chem.*, **80**, 183 (1909); Willgerodt and Merk, *ibid.*, **80**, 192 (1909); Willgerodt and Hambrecht, *ibid.*, **81**, 74 (1910); Willgerodt and Scholtz, *ibid.*, **81**, 382 (1910); Willgerodt and Albert, *ibid.*, **84**, 387 (1911). Also Weitzenbock and Lieb, *Monatsh.*, **33**, 564 (1912); Cook, *J. Chem. Soc.*, 2524 (1931); Mosettig and van de Kamp, THIS JOURNAL, **55**, 3442 (1933).

(7) Cook, Haslewood and Robinson, *J. Chem. Soc.*, 667 (1935).

(8) Willgerodt and Merk (ref. 6) heated phenyl isobutyl ketone with yellow ammonium sulfide and isolated in 14–15% yield a substance melting at 118° and regarded as α-methyl-γ-phenylbutyramide. We prepared the ketone both by the Friedel and Crafts reaction (56%) [Claus, *J. prakt. Chem.*, **46**, 490 (1892)] and from benzamide and isobutyl bromide (39%) and tried the Willgerodt reaction under various conditions. The best yield of amide, isolated as glistening plates, m. p. 121–122° was 1.8%. Saponification and conversion to the anilide gave fine needles, m. p. 137–138°, with softening at 130°. Krollpfeiffer and Schäfer [*Ber.*, **56**, 620 (1923)] report the m. p. 140° for the anilide of α-methyl-γ-phenylbutyric acid, while the anilide of the β-methyl isomer is given as 101° [Anschütz and Motschmann, *Ann.*, **407**, 88 (1915)].

(9) Fieser, Joshel and Seligman, THIS JOURNAL, **61**, 2134 (1939).

chromatographic adsorption, distillation and crystallization, methyl 7-cholanthroate was isolated as a nicely crystalline product of sharp melting point in small yield (4.5%). Hydrolysis gave 7-cholanthroic acid (X), the alkali salts of which are moderately soluble in water, and the substance is being tested for carcinogenic activity. While the pure acid seemed rather resistant to decarboxylation by heating with basic copper carbonate (at least on a micro scale), the crude acidic product of the cyclization was converted by this catalyst into cholanthrene, identified by mixed melting point determination and by the preparation of the picrate. The yield of cholanthrene from the amino acid IX was 8.1%.

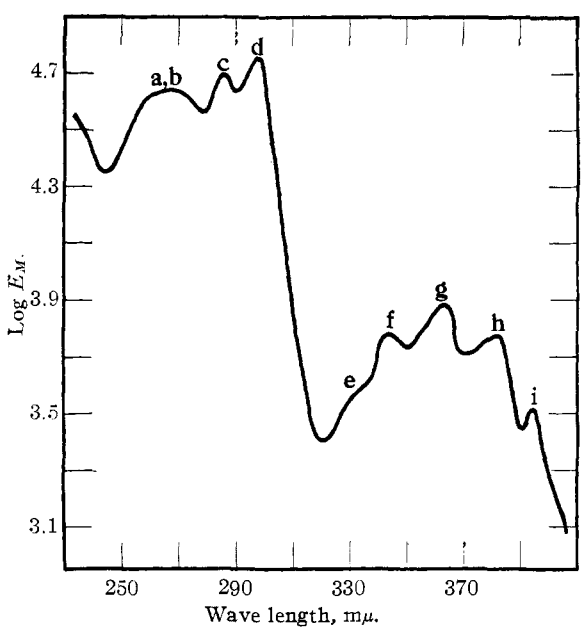



Fig. 1.—Methyl 7-cholanthroate in hexane.

The ultraviolet absorption spectrum of methyl 7-cholanthroate (Fig. 1), kindly determined by Dr. R. N. Jones, corresponds in general form and detail with that of cholanthrene,[10] although some resolution is lacking. A comparison of the wave lengths and intensities of the principal maxima with those of cholanthrene is given in Table I.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA

| Maxima | Cholanthrene λ, mμ | Cholanthrene Log $E_M$ | Methyl 7-cholanthroate λ, mμ | Methyl 7-cholanthroate Log $E_M$ |
|---|---|---|---|---|
| a, b | (265.5) | 4.6 | 265.5 | 4.65 |
| c | 284.5 | 4.8 | 285.5 | 4.69 |
| d | 295 | 4.9 | 297.5 | 4.75 |
| e | 328 | 4.6 | (328) | (3.53) |
| f | 342 | 3.8 | 344 | 3.78 |
| g | 358 | 4.0 | 362 | 3.89 |
| h | 377 | 3.8 | 381 | 3.77 |
| i | (388) | (3.5) | 394 | 3.52 |

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

## Experimental Part[11]

**Acylation of Acenaphthene with Phenylacetic Acid.**—A mixture of 10 g. of the hydrocarbon, 9.3 g. of phenylacetic acid, and 130 g. of anhydrous hydrogen fluoride was allowed to stand at room temperature in a platinum container for ten and one-half hours and poured onto ice. The greenish, amorphous precipitate was ground in a mortar with sodium carbonate solution to neutralize adhering acid, then washed and dried, giving 16.9 g. of gray-green powder, m. p. 65–95°. Repeated crystallization from benzene and from ethyl acetate–hexane gave **3-phenylacetoacenaphthene,** m. p. 111.5–113°, in 30% yield. The picrate, prepared in alcohol and crystallized from benzene–hexane, formed somewhat unstable, yellow-orange needles, m. p. 107.5–108.5°. The ketone recovered from the picrate with the use of an alumina adsorption tower crystallized from ethyl acetate–hexane in the form of colorless prisms, m. p. 113.5–114°.

*Anal.* Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 87.96; H, 5.99.

By oxidation of 1 g. of this ketone in dioxane with sodium hypoiodite solution there was obtained 121 mg. of 3-acenaphthoic acid, m. p. 218–219°. The m. p. was not raised by recrystallization from alcohol and the acid showed no depression with an authentic sample.

The residual ketonic mixture on repeated crystallization afforded a small amount of substance melting at 73–90° which was converted into the picrate in benzene. After crystallization from ethyl acetate–hexane, this derivative was obtained as brilliant yellow needles which seemed to undergo a change in form at 130.5–131° and melted at 133–134°. **1-Phenylacetoacenaphthene** was recovered from the picrate with the use of benzene and ammonia solution and crystallized from benzene–hexane. It formed large, pale yellow prisms, m. p. 81–81.5°.

*Anal.* Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.04; H, 5.99.

Oxidation of 200 mg. as above gave 59 mg. of crude acid, m. p. 240–250°. Crystallized from alcohol, the sample melted at 251–252.5° and did not depress the m. p. of authentic 1-acenaphthoic acid.

***o*-Bromophenylacetic Acid.**[12]—The diazomethane formed by dropping 55 cc. of nitrosomethylurethan in 55 cc. of ether into 60 cc. of a warm saturated solution of potassium hydroxide in absolute alcohol covered with ether (20 cc.) was distilled through a vertical coil condenser and absorbed in cold absolute ether. After dilution to 800 cc. with cold ether, 21.4 g. of *o*-bromobenzoyl chloride (b. p. 103–104° at 5 mm.) was added in ether with mechanical stirring at 0° during one hour. After five hours at room temperature a fluffy precipitate was removed by filtration and the ether evaporated in vacuum, leaving 22.8 g. of a brownish, oily, lachrymatory product, m. p. 36–41°. Crystallized by concentrating an ether–hexane solution of

(11) All final melting points are corrected.

(12) Following the procedure of Litvan and Robinson, *J. Chem. Soc.*, 1997 (1938).

the product in vacuum and cooling, this gave 14.6 g. (66.5%) of yellow and not appreciably oily **diazomethyl-o-bromophenyl ketone**, m. p. 42–43° (gas evolution). The mother liquor material was largely oily (6.2 g.). A solution of the crystallized diazo ketone (14.6 g.) in technical dioxane was added in one-half hour with stirring to a suspension of 16 g. of silver oxide in 800 cc. of water containing 24 g. of sodium thiosulfate at 60–65°. After one-half hour more the evolution of gas had practically ceased and the mixture was made alkaline with 25 cc. of 10% sodium hydroxide and filtered. The filtrate was washed with benzene, acidified with dilute nitric acid, and extracted with ether. On concentrating the extract and adding hexane the product separated as an oil. By slowly acidifying a solution of the acid in dilute alkali, 11.4 g. (81.7% from the diazo ketone) of *o*-bromophenylacetic acid[13] was obtained as an odorless, pale yellow, crystalline powder, m. p. 103–105°. Treatment with Norit in an aqueous solution containing a very slight excess of sodium carbonate gave pure white acid, m. p. 103.5–105.5°, and on two crystallizations from benzene–hexane it formed clusters of jagged prisms, m. p. 105–106°.

The impure diazo ketone (6.2 g.) gave 3 g. of yellow acid, m. p. 98–102°. Crystallization failed to effect much purification, but treatment with Norit in an aqueous solution containing little excess soda and precipitation gave 1.72 g. of pure white powder, m. p. 103.5–105.5°. The total yield of satisfactory acid was 13.1 g., a 62.5% over-all yield from the acid chloride (prepared from *o*-bromobenzoic acid in 98% yield with thionyl chloride).

**Acenaphthene and *o*-Bromophenylacetic Acid.**—The condensation of 1.43 g. of the hydrocarbon with 2 g. of the acid in hydrogen fluoride (85 g.), conducted at room temperature for one and one-half hours, gave 3.05 g. of neutral, light yellow powder, m. p. 85–102°. Little separation was effected by crystallization as such or through the oxime, but crystallization as the picrate and dissociation of alumina afforded small amounts of a white powder, m. p. 128–129.5°, and of tiny white needles, m. p. 122–123°, from the less and more soluble fractions, respectively. Another portion processed through the trinitrobenzene derivatives gave light yellow prisms, m. p. 128–129.5°, and light yellow needles, m. p. 110.5–112.5°. Since none of these substances was obtained in practical quantity they were not characterized further.

**1-Acetoacenaphthene** was prepared in the pressure vessel as described by Fieser and Hershberg.[2b] The crude product from two 80-g. batches of commercial "95%" acenaphthene was collected on a Büchner funnel (cold room) and then ground in a mortar three times with water, the material each time being collected on a funnel and pressed well to force out as much oil as possible. Two similar washings were made with sodium carbonate solution, and after a final washing with water the product was dried partially by exposure to air and then fully dried by adding benzene and distilling. Distillation gave 143.4 g. of ketone mixture boiling largely at 181–183° (3 mm.), m. p. 80–95°, and there was about 10 g. of tarry residue. Crystallization at room temperature from 400 cc. of methanol and then from 750 cc. of this solvent[3] yielded 87.1 g. of the 1-isomer, m. p. 103–105°, and 5 g. of equally good material was obtained by working the second mother liquor; total yield 45% (calculated for pure acenaphthene).

**1-Acenaphthylacetic Acid (VII). (a) Arndt–Eistert Reaction.**—1-Acenaphthoic acid and its chloride were prepared according to Fieser and Cason[3] with closely agreeing results. Nitrosomethylurethan (24.3 cc.) in absolute ether (198 cc.) was dropped into 42 cc. of a solution prepared from 3 g. of sodium and 50 g. of glycol at 50°[14] and the distillate collected in a flask cooled in ice. After flushing the apparatus with ether the solution was diluted to about 275 cc. with absolute ether and a solution of 7.59 g. of 1-acenaphthoyl chloride (m. p. 108–110.5°) in absolute ether (87 cc.) and purified dioxane (44 cc.) was added during 50 minutes while stirring and cooling in ice. After stirring for two and one-quarter hours longer at room temperature, the precipitated light yellow **diazo ketone** was collected (4.01 g., m. p. 141–142° dec.) and the filtrate was concentrated to about 4 cc. and cooled, giving 3.24 g. of orange-yellow material, m. p. 137–141° (crude yield 93%). The combined product was taken up in 70 cc. of technical dioxane and the solution, filtered from a slight residue (0.1 g.), was added dropwise in one hour to a stirred suspension at 60–70° of 8.2 g. of silver oxide in 435 cc. of water containing 21.4 g. of sodium thiosulfate. After stirring for one and one-half hours longer 0.5 g. of Norit was added and the mixture was cooled and filtered and the filtrate acidified with dilute acetic acid (hydrochloric or nitric acid caused darkening of the precipitate). The precipitated 1-acenaphthylacetic acid (5.96 g.) softened at 150° and melted at 157–165°. Crystallization from methanol (15 cc.) gave pale yellow needles, m. p. 155.5–160°; yield 4.74 g. (63.5% from the acid chloride). After crystallization of the potassium salt from absolute alcohol the recovered acid melted at 158–159.5°, and repeated crystallization from benzene–hexane gave fine white needles, m. p. 163.5–164.4°.

*Anal.* Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.87; H, 5.46.

(b) **Willgerodt Reaction.**—When 1-acetoacenaphthene was submitted to the reaction under the conditions specified by Willgerodt and Merk[6] (five to six hours at 200–220°) the material was badly decomposed and little amide could be isolated. After a number of variations had been tried the best results were obtained as follows. A solution of 1 g. of sulfur in 10 g. of a solution of ammonium sulfide prepared by saturating concentrated ammonia solution with hydrogen sulfide was sealed in a tube with 2 g. of 1-acetoacenaphthene and 8 cc. of purified dioxane and the mixture was heated at 160° for twelve hours. The dark solid product (m. p. 185–205°, a few yellow plates present melted at 205°) was collected and refluxed for four hours with 50 cc. of 15% sodium hydroxide. Water (50 cc.) and Norit (0.25 g.) were added and the solution was filtered hot and treated with dilute hydrochloric acid until just weakly alkaline, when a small amount of sludge separated and could be removed by filtration. Acidification of the filtrate gave 1.37 g. of 1-acenaphthylacetic acid, m. p. 159–162°. A further quantity was recovered from the ammonium sulfide filtrate. After acidifying and collecting the coagulated sulfur the filtrate was concentrated and a little gummy solid

(13) Jackson and White, *Am. Chem. J.*, **2**, 316 (1880).

(14) Meerwein and Burneleit, *Ber.*, **61**, 1845 (1928).

obtained. Extraction of the combined gum and sulfur with bicarbonate solution gave 80 mg. of crude acid. The combined material on crystallization from dilute alcohol afforded 1.24 g. (57%) of fine, light orange needles, m. p. 163–165°. On recrystallization with liberal use of Norit the substance formed pure white needles, m. p. 167.6–168.2° (slight softening at 163°).

*Anal.* Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.06; H, 5.77.

In larger runs conducted in an autoclave the reaction mixture was charged into a 500-cc. round-bottomed flask connected by means of a hemispherical ground-glass joint (which effectively prevented freezing) to a spiral made from about 60 cm. of 1-mm. capillary tubing.[15] Nitrogen (at 500–1000 lb. (33–67 atm.) pressure) was admitted, and allowed to escape, very slowly. From 19.2 g. of 1-acetoacenaphthene, 96 g. of ammonium sulfide solution, 9.6 g. of sulfur and 77 cc. of dioxane, heated for eighteen hours at 175–180°, there resulted 6.8 g. (33%) of reddish-brown, semicrystalline amide. The oily filtrate was extracted with benzene and the aqueous layer on acidification and extraction of the precipitate as above gave 426 mg. (2.1%) of yellow acid, m. p. 159–160°. The benzene solution was evaporated and the residual oil refluxed for four hours with 300 cc. of 15% sodium hydroxide, giving, on acidification of the separated aqueous phase, 358 mg. (1.7%). The combined yield of crude acid and amide was thus 36.8%. For the complete hydrolysis of as much as 20 g. of the crude amide a refluxing period of six hours was required.

The unsaponified oil after washing and drying distilled at 160–163° (6 mm.), yielding 8.3 g. (46.7%) of **1-ethylacenaphthene** as a pale yellow oil which crystallized on cooling. This was redistilled and crystallized from methanol, giving colorless needles, m. p. 34.8–35.1° (not changed by recrystallization).

*Anal.* Calcd. for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.21; H, 7.89.

The **picrate**, purified to constant m. p. by crystallization from absolute alcohol–hexane, formed brilliant red needles, m. p. 104.7–105.1°. The hydrocarbon could be extracted from the picrate with hexane, and after passing the solution through an alumina tower, the recovered hydrocarbon crystallized from methanol as needles, m. p. 33.5–34.5°. For the hydrocarbon and its picrate Cook, Haslewood and Robinson[7] give the melting points 30° and 102–102.5°.

In a run conducted as above except that the temperature was kept at 170° for eighteen hours, the yield of crude amide was 22% and of ethylacenaphthene 65%. With the same reaction time but at 188–190° the corresponding yields were 29 and 43%. On increasing the amount of ammonium sulfide solution (139 g.) and dioxane (120 cc.) and heating for eighteen hours at 163–164° the yield of amide dropped to 7.5% and ethylacenaphthene was obtained in 67.5% yield.

**α-(*o*-Chlorobenzal)-1-acenaphthylacetic Acid (II, R = $CO_2H$; X = Cl).**—1-Acenaphthylacetic acid was titrated in methanol to a phenolphthalein end-point with 0.5 *N* potassium hydroxide in methanol; the solvent was evaporated completely and the residue dried at 100° in vacuum. This salt (250 mg.) was refluxed with 162 mg. of freshly distilled *o*-chlorobenzaldehyde, 1 cc. of acetic anhydride and one drop of pyridine at a bath temperature of 180° for twenty-four hours. Water (75 cc.) and excess sodium bicarbonate were added and on refluxing for about two hours only a small amount of tar remained undissolved. After extracting this with benzene, acidification gave 289 mg. of acid, m. p. 175–200°. Crystallization from dilute acetic acid (Norit) gave 145 mg. of bright yellow needles, m. p. 214–216°, and 45 mg. of slightly lower m. p. (total yield 55%). After further crystallizations from dilute alcohol, dilute acetic acid or chloroform–hexane the acid melted constantly at 221.5–223.5° with slight previous softening.

*Anal.* Calcd. for $C_{21}H_{15}O_2Cl$: C, 75.33; H, 4.52. Found: C, 75.20; H, 4.49.

Following Hewett's procedure,[4] cyclization was attempted by fusing the acid (0.4 g.) with 85% potassium hydroxide (3 g.) at a bath temperature of 254° (cor.) but only small amounts of starting material could be recovered. At slightly lower temperatures the reaction product gave a strong Beilstein test and at slightly higher temperatures the bulk of the product was insoluble in alkali.

**α-(*o*-Nitrobenzal)-1-acenaphthylacetic Acid (VIII).**—The potassium salt from 24.9 g. of 1-acenaphthylacetic acid was heated with 21.7 g. of *o*-nitrobenzaldehyde and 250 cc. of acetic anhydride for three hours at a bath temperature of 125–130° and the mixture was poured into 1200 cc. of water and allowed to stand overnight. The orange-yellow product was precipitated twice as the potassium salt from aqueous potassium carbonate, the somewhat oily salt being washed each time on the filter with half-saturated potassium carbonate solution. The liberated acid without being dried was dissolved in acetic acid, and after Norit treatment the solution was concentrated to 250 cc. and allowed to cool, when 23.8 g. (59%) of yellow, crystalline product separated, m. p. 239–241°. Recrystallized from alcohol and from acetic acid, the acid formed shiny, pale yellow needles, m. p. 244.5–244.9°, dec. (black melt).

*Anal.* Calcd. for $C_{21}H_{15}O_4N$: N, 4.06; neut. equiv., 345. Found: N[16] (Kjeldahl), 4.17; neut. equiv., 346.

**α-(*o*-Aminobenzal)-1-acenaphthylacetic Acid (IX).**—Following Cassaday and Bogert,[17] a solution of 15.8 g. of the nitro acid in 120 cc. of water and 15 cc. of ammonia solution was added during five minutes to a boiling mixture of 80 g. of ferrous sulfate crystals, 261 cc. of water and 20.4 cc. of ammonia solution. While boiling, and with the addition of a little octyl alcohol to suppress frothing, 158 cc. of ammonia solution was added during twenty minutes followed by 41 cc. in the next fifty-five minutes. After cooling, Celite was added and the cake obtained on filtration was extracted six times with boiling water containing ammonia. After treatment of the combined solutions with Norit and Celite the still dark filtrate on acidification with dilute acetic acid (avoiding an excess) deposited the acid as a gum which soon changed to a yellow solid. For crystallization the acid was dissolved in alcohol and

(15) Grosse, THIS JOURNAL, **60**, 212 (1938).

(16) Microanalysis by Lyon Southworth.

(17) Cassaday and Bogert, THIS JOURNAL, **61**, 2463 (1939).

water was gradually added at the boiling point until a considerable quantity of well formed crystals had separated. The substance was thus obtained as brownish-yellow prismatic plates, m. p. 227–229°; yield 11.0 g. (76%).

Reduction proceeded less satisfactorily when a suspension of 2 g. of the nitro acid and 25 mg. of Adams catalyst in 33 cc. of alcohol was shaken with hydrogen. After eight hours 94% of the theoretical amount of hydrogen had been absorbed. After dilution with water the product was extracted with benzene and the filtered solution extracted with bicarbonate. Acidification with dilute acetic acid gave 963 mg. (53%) of amino acid, m. p. 224–226°. Recrystallization from alcohol–water as above yielded pale yellow prisms, m. p. 229–230.5°, and further crystallizations seemed to cause slight deterioration.

*Anal.*[16] Calcd. for $C_{21}H_{17}O_2N$: N (Kjeldahl), 4.44. Found: N, 4.41.

Concentration of the extracted benzene solution yielded 304 mg. (18%) of a colorless, neutral substance. After repeated crystallization from dioxane and acetic acid fine white needles were obtained, m. p. 236.4–238.4° dec. (black liquid). The substance seemed resistant to hydrolysis with acid or alkali; it was characterized only by analysis[16]: C, 83.82; H, 5.54; N (Dumas), 4.85.

In another experiment a trace of another neutral by-product, m. p. 278–279.5°, was also obtained (see below).

**Methyl 7-Cholanthroate.**—A solution of 8 g. of the amino acid in 200 cc. of purified dioxane was treated with 1.9 cc. of sulfuric acid in 100 cc. of dioxane and the voluminous yellow solid which precipitated was brought into solution by the addition of dioxane (300 cc.) and alcohol (500 cc.) and warming gently. After cooling to room temperature 4.8 cc. of isoamyl nitrite in 10 cc. of dioxane was added with stirring in ten minutes.[17,18] No temperature rise was observed, but the solution took on a dark red color and a test sample gave an intense red coloration with alkaline β-naphthol. After stirring for one hour a solution of 26 g. of sodium hypophosphite in 26 cc. of water was added all at once, followed by the Gattermann copper paste[19] prepared from 31 g. of copper sulfate crystals and 75% of the theoretical amount of zinc. Gas was evolved at once. The mixture was stirred in a bath at 50° for one hour, the coupling test being negative after fifteen minutes. Potassium carbonate solution was added to the point of alkalinity and about 1 liter of solvent was removed under vacuum. The gum separating was brought into solution by the addition of water, and after filtration from the copper the solution was poured into 200 cc. of water and 25 cc. of concentrated hydrochloric acid. The precipitated acid was collected, dried, dissolved in 325 cc. of purified dioxane and a sediment was removed by filtration. The very dark filtrate was cooled and treated with an ethereal solution of diazomethane from 23 cc. of nitrosomethylurethane, the large excess of reagent apparently being all consumed. Evaporation of the solvent left a brown powder insoluble in alkali. This was dissolved in benzene and the solution was filtered from 1.62 g. of gelatinous material, concentrated, and passed through a tower of alumina–Celite (1:1). The first filtrate was very black and eventually was discarded. The adsorbed material was eluted with benzene containing about 10% of methanol until the filtrate no longer showed appreciable color, and after evaporation of the solvent distillation at 1 mm. yielded 1.57 g. of thick, dark oil, which was taken up in benzene. The solution, filtered from a pale yellow residue (A, 64 mg.) and concentrated to a small volume, deposited clusters of dark needles, and on recrystallization from benzene methyl 7-cholanthroate was obtained as pale yellow needles, m. p. 156–158° (293 mg.). The mother liquors afforded 67 mg. of similar material; total yield 360 mg. (4.5%). On two recrystallizations from alcohol the substance formed golden-yellow needles, m. p. 159.0–159.2°, exhibiting a dull blue-green fluorescence in benzene.

*Anal.* Calcd. for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.54; H, 5.30.

Material eluted from the column using higher concentrations of alcohol gave a black oil on distillation and this left a yellowish residue (B, 66 mg.) on treatment with benzene; concentration of the solution gave only tars.

The total benzene-insoluble product (A and B, m. p. 270–275°), after repeated crystallization from acetic acid–water (Norit) afforded a small amount of almost colorless needles, m. p. 280.3–281.2°, dec. (black melt), which gave no depression when mixed with the high melting by-product of the catalytic reduction of the nitro acid VIII. The substance can be dissolved in boiling alkali but after precipitation does not redissolve. The composition appears to be about the same as that of the other unidentified by-product of the hydrogenation (found[16]: C, 84.15; H, 5.01; N (Dumas), 4.75).

**7-Cholanthroic Acid (X).**—The pure ester (207 mg.) was refluxed for one and one-half hours with 65 cc. of 10% alcoholic potassium hydroxide solution. Most of the solvent was removed under vacuum, the residue was diluted with 200 cc. of water and the filtered solution poured into 200 cc. of water containing 15 cc. of concentrated hydrochloric acid. The precipitated acid, collected after coagulation by heating, was obtained as a pale yellow powder, m. p. about 253–256° (195 mg.). The material seemed to deteriorate slightly in acetic acid or alcohol but could be crystallized satisfactorily from a large volume of benzene. Acid so purified when heated in a sealed capillary showed a fairly constant decomposition point of 258.5–261°, after incipient sublimation at 255°.

*Anal.* Calcd. for $C_{21}H_{14}O_2$: C, 84.55; H, 4.73. Found: C, 84.36; H, 4.78.

When a small sample was ground with basic copper carbonate and melted in an evacuated tube, a white sublimate appeared on the upper walls and was found to melt above 200°, indicating that the pure acid is not readily decarboxylated by this method. On heating 17 mg. of slightly impure acid in high vacuum ($10^{-3}$ mm.) at 200° for nineteen hours, 14 mg. of acid, m. p. 255–259°, sublimed leaving a dark residue.

**Cholanthrene.**—Following a simplified procedure, 1 g. of the amino acid was diazotized as above with isoamyl nitrite and after shaking for only about two minutes Gattermann copper was added and decomposition was conducted in a bath at 50° for twenty-five minutes. The crude acid precipitated from carbonate solution was

(18) Rüggli and Staub, *Helv. Chim. Acta*, **20**, 37 (1937).

(19) Gattermann, *Ber.*, **23**, 1219 (1890).

ground with 25 mg. of basic copper carbonate and heated under vacuum in a bath which was eventually brought to a temperature of 300°. The dark distillate (294 mg.) was extracted three times with cold absolute alcohol and the undissolved material taken up in benzene. After treatment with Norit and concentration, 65 mg. (8.1%) of light brown crystals separated. Purification by adsorption of impurities on alumina gave a yellow crystalline powder, m. p. 167.5–168.5°, which gave no depression when mixed with known cholanthrene, m. p. 166.5–168.5°. The picrate agreed in m. p. and appearance with the specimen described by Cook, Haslewood and Robinson.[7]

## Summary

1-Acetoacenaphthene was converted to 1-acenaphthylacetic acid via 1-acenaphthoic acid by the Arndt–Eistert reaction and, more conveniently, by the Willgerodt process of heating the ketone with yellow ammonium sulfide. The acetic acid was condensed successfully with both *o*-chloro and *o*-nitrobenzaldehyde, but only the second of the products could be utilized for effecting a phenanthrene ring closure. Although the Pschorr reaction proceeded very poorly, the 7-carboxy derivative of cholanthrene was isolated through the ester in quantity sufficient for an investigation of its possible biological actions.

The hydrogen fluoride acylation of acenaphthene with phenylacetic acid and *o*-bromophenylacetic acid does not provide a practical route to intermediates suitable for the synthesis of cholanthrenes.

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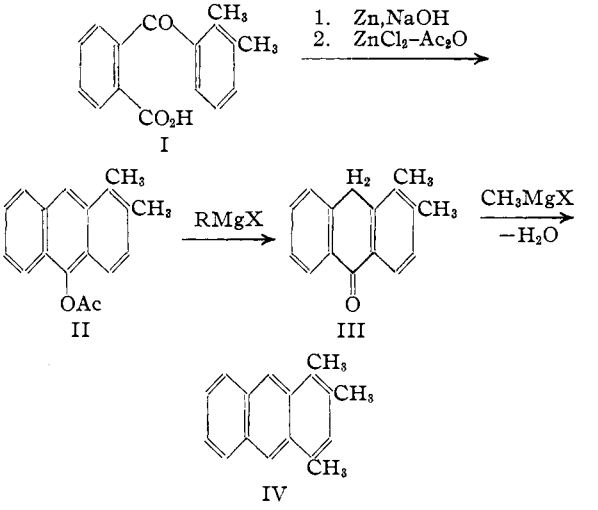
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# *meso*-Alkyl Anthracenes

BY LOUIS F. FIESER AND THOMAS G. WEBBER

In continuation of previous studies of model compounds structurally related to the more potently active carcinogens,[1] we sought to synthesize certain additional substituted 1,2-dialkyl anthracenes of types corresponding to known 1,2-benz derivatives of marked carcinogenic activity. The 1,2-dimethyl and 1,2-cyclopenteno derivatives of 5,10-aceanthrene were synthesized in earlier work[2] for comparison with cholanthrene, and the cyclopenteno compound was found by Shear (see ref. 1) to have definite if weak carcinogenic properties. It was hoped in the present work to obtain 1,2,10-trimethylanthracene and 1,2,9,10-tetramethylanthracene for comparison with 10-methyl-1,2-benzanthracene[3] and 9,10-dimethyl-1,2-benzanthracene,[4] respectively. The trimethyl compound was synthesized without difficulty, but the method tried for the preparation of the higher homolog proved unsatisfactory. Badger, Cook and Goulden[5] have recently reported an unsuccessful attempt to synthesize the same hydrocarbon by another method.

1,2,10-Trimethylanthracene was synthesized starting with the keto acid I[5] from *vic.*-bromo-*o*-xylene and phthalic acid. After reduction with zinc and alkali, cyclization with zinc chloride and acetic acid–anhydride[6] gave the anthranyl acetate (II), and on cleavage by the Grignard reagent the




anthranol isomerized readily to the anthrone. A methyl group was then easily introduced at the 10-position. As with anthracene and a number of its derivatives,[7] the yellow trimethyl compound IV forms a colorless dimer when exposed to sunlight in solution.

A projected synthesis of the desired tetramethyl

(1) For summary and review, see Fieser, *Am. J. Cancer*, **34**, 37 (1938).
(2) Fieser and Hershberg, THIS JOURNAL, **59**, 394 (1937).
(3) Fieser and Newman, *ibid.*, **58**, 2376 (1936).
(4) Bachmann and Chemerda, *ibid.*, **60**, 1023 (1938).
(5) Badger, Cook and Goulden, *J. Chem. Soc.*, 16 (1940).
(6) Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).
(7) Houben, "Das Anthracen und die Anthrachinone," Verlag Georg, Thieme, Leipzig, 1929, p. 133.