Anal. Calcd. for $C_{16}H_{14}O_3N_2$: N, 9.93. Found: N, 9.86, 9.89.

Pharmacological tests of this new barbituric acid were made on white rats. For this purpose two per cent. solutions of the sodium salt of the acid were injected intraperitoneally into the test animals, which were starved for twenty-four hours previous to the injections. For each dose three to five animals were used. The minimum hypnotic dose in mg. per kg. of rat was 300 mg. The minimum anesthetic dose was 400 mg. The minimum lethal dose was 450 mg., the therapeutic index of the compound being, therefore, 1.12. On the basis of these results this barbituric acid is not as satisfactory as phenylethylbarbituric acid.

I am indebted to Horace Shonle of the Lilly Research Laboratories, Eli Lilly & Co., for the pharmacological work published in this paper.

Summary

1. The methyl ester of α-naphthylacetic acid has been condensed with dimethyl oxalate to produce α-naphthyldimethylmalonate, and this ester alkylated to form α-naphthylethyldimethylmalonate.

2. α-Naphthylethyldimethylmalonate has been condensed with urea in sodium ethylate solution to form 5-α-naphthyl-5-ethylbarbituric acid.

3. Tests have shown that this new barbituric acid possesses hypnotic properties but is not as satisfactory as 5-phenyl-5-ethylbarbituric acid.

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Studies in the Phenanthrene Series. V. 9-Acetylphenanthrene. Reduction Products of 2-, 3- and 9-Acetylphenanthrenes[1]

BY ERICH MOSETTIG AND JACOB VAN DE KAMP

Willgerodt and Albert[2] obtained by the action of acetyl chloride on phenanthrene a compound to which they assigned the formula of 9-acetylphenanthrene, basing this structure on the carbon–hydrogen analysis, formation of a phenylhydrazone and an oxime, and the chromic acid oxidation to phenanthrene-9,10-quinone. In a repetition[3] of this Friedel–Crafts reaction under the experimental conditions of Willgerodt and Albert, we obtained a mixture of 2- and 3-acetylphenanthrenes. When nitrobenzene was used as a solvent instead of carbon disulfide, the difference was only quantitative, and the 2- and 3-isomers could be isolated in a ratio of about 1:4. In spite of a careful investigation of the reaction mixture another isomer could not be detected. Neither the 2- nor the 3-ketone

(1) This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc., and the Rockefeller Foundation.

(2) Willgerodt and Albert, *J. prakt. Chem.*, [2] **84**, 383 (1911).

(3) Mosettig and van de Kamp, THIS JOURNAL, **52**, 3704 (1930).

agreed in properties with the compound described by Willgerodt and Albert. It was therefore of interest to synthesize the 9-acetylphenanthrene in a way which would leave no doubt about its constitution.

The application of Claisen's condensation to phenanthrene-9-carboxylic acid methyl ester and ethyl acetate—whereby a large excess of the latter reagent was necessary because of the preponderant formation of acetoacetic ester over that of phenanthroylacetic ester—and the following scission of the keto acid ester with dilute sulfuric acid gave the desired 9-acetylphenanthrene in a yield of about 80% of the theoretical. As can be seen from Table I, this ketone is entirely different in its properties from the "9-acetylphenanthrene" described by Willgerodt and Albert.

Whereas there is an obvious resemblance in the meso positions of phenanthrene and anthracene, in their behavior toward nitric acid and halogens, in both of which the relative stability of the primary addition products formed is characteristic, in the Friedel–Crafts reaction a similarity in the reactivity of the 9- or 10-positions in these two hydrocarbons can scarcely be claimed. By the action of benzoyl chloride,[4] cyanogen bromide,[5] oxalyl chloride,[6] and phthalic anhydride[7] on anthracene, only the resulting 9-derivatives were isolated.

With phenanthrene the corresponding reactions appear to be more complicated. Our attempts to carry out Karrer's nitrile preparation with cyanogen bromide were practically fruitless.[8] The action of oxalyl chloride on phenanthrene, first described by Liebermann and Zsuffa,[9] does not give phenanthrene-9-carboxylic acid as the main product, as these authors, apparently influenced by their results on anthracene, report. but rather phenanthrene-3-, 2- and 9-carboxylic acids in the ratio 75:18:4.[8] The entering of the benzoyl group in the 9-position, according to Willgerodt and Albert,[10] has not been proved and is doubtful. The action of phthalic anhydride on phenanthrene[7] apparently results in an inseparable mixture.[11] The reaction of diethylmalonyl chloride with phenanthrene[12] as well as with retene, yielding phenanthrene- and retene-diethyl indandiones, respectively, leaves the 9- and 10-positions unattacked, but remarkably enough in anthracene also the diethylmalonyl group is not linked to the 9- and 10-positions. The action of the *o*-toluyl chloride on phenanthrene[13] yields a mixture of 9-, 2- and 3-ketones, the 9-isomer being formed in the largest, the 3-isomer in the smallest, amount.

Although these experimental facts, quoted for comparison, do not allow strict conclusions (since in some cases the reaction mixture was not worked up entirely, and in other cases the experimental conditions were different) the assumption seems to be justified that in the Friedel-Crafts reactions only in the case of anthracene the meso positions seem to be generally preferred to other positions in the molecule.

The greater reactivity of the meso positions in anthracene in comparison with the 9,10-positions in phenanthrene is also shown by the ability of anthracene to add benzo-

(4) Krollpfeiffer, *Ber.*, **56**, 2360 (1923).
(5) Karrer and Zeller, *Helv. Chim. Acta*, **2**, 482 (1919).
(6) Liebermann and Zsuffa, *Ber.*, **44**, 202 (1911).
(7) Heller, *ibid.*, **45**, 665 (1912).
(8) Mosettig and van de Kamp, THIS JOURNAL, **54**, 3328 (1932).
(9) Liebermann and Zsuffa, *Ber.*, **44**, 202 (1911).
(10) Willgerodt and Albert, *J. prakt. Chem.*, [2] **84**, 383 (1911).
(11) *Cf.* Clar, *Ber.*, **62**, 350 (1929).
(12) Freund and Fleischer, *Ann.*, **373**, 291 (1910).
(13) Ref. 11 and p. 1574.

quinone[14] and maleic anhydride[15] at the meso positions whereas phenanthrene is not attacked at all.

The results of the Friedel-Crafts reaction with acid chlorides on anthracene, patented by the I. G. Farbenindustrie, A.-G., are of special interest. Depending on the conditions, α-, β- or ms-acetylanthracenes, the latter at lower temperature and with solvent, were obtained.[16] When the ms-acetylanthracene is treated in nitrobenzene solution with aluminum chloride, migration of the acetyl group takes place and β-acetylanthracene is formed at 40°.[17] For an analogous reason, the absence of 9-acetylphenanthrene in the reaction mixture of the Friedel–Crafts reaction of acetyl chloride on phenanthrene might have been explained. However, when 9-acetylphenanthrene was treated with aluminum chloride under the conditions imposed in this Friedel-Crafts reaction, and even under stronger conditions (aluminum bromide instead of aluminum chloride, higher temperature (50°), and longer time (four days)), the starting material was recovered practically unchanged.

Willgerodt developed a method for converting fatty–aromatic ketones into acids with the same number of carbon atoms, by treating the ketones at high temperatures with yellow ammonium sulfide,[18] and applied this reaction also to his "9-acetylphenanthrene." Because of the small yields obtained, however, we found this method to be practically useless for the preparation of the phenanthrylacetic acids from 2-, 3- and 9-acetylphenanthrene. The acids obtained in this way proved nevertheless to be identical with those prepared in the meantime in a convenient way from phenanthrene-2-, 3- and 9-aldehydes.[19]

The reduction of the acetylphenanthrenes with zinc in acetic acid, in ammoniacal and alkaline alcoholic solutions, and with aluminum amalgam in a neutral medium, gave hardly any carbinol, the formation of complex compounds, presumably to a large extent pinacols, predominating. The catalytic reduction with platinum oxide in alcohol leads quantitatively to the carbinols, with the exception of the 3-isomer, where besides the carbinol about 10% of a compound is formed whose nature could not be ascertained. The high-pressure hydrogenation with copper–chromium–barium oxide catalyst appears to be most convenient, particularly for the preparation of the phenanthrylmethylcarbinols on a larger scale. This catalyst, prepared and employed first by Adkins and Connor,[20] is, as the authors point out, of particular value for selective hydrogenation, being inactive toward benzenoid rings. At temperatures around 100° the ketones were smoothly reduced to the carbinols; at temperatures of about 150° the reduction proceeded to the corresponding ethylphenanthrenes. In the

(14) Kremann and co-workers, *Monatsh.*, **43**, 269 (1922).

(15) Clar, *Ber.*, **64**, 1676, 2194 (1931); **65**, 846, 1411 (1932). *Cf.* Diels and Alder, *Ann.*, **486**, 191 (1931).

(16) I. G. Farbenindustrie, A.-G., German Patents 492,247 and 493,688; *Chem. Abstracts*, **24**, 2472, 2757 (1930)

(17) I. G. Farbenindustrie, A.-G., German Patent 499,051; *Chem. Abstracts*, **24**, 4055 (1930).

(18) Willgerodt, *Ber.*, **20**, 2467 (1887); **21**, 534 (1888); *J. prakt. Chem.*, [2] **80**, 183, 192 (1909); [2] **81**, 74 (1910).

(19) Mosettig and van de Kamp, THIS JOURNAL, **55**, 2995 (1933).

(20) Adkins and Connor, *ibid.*, **53**, 1091 (1931).

reduction of 3-acetylphenanthrene, besides the carbinol, a product was formed that could not be obtained uniform and pure. We prepared the 3-carbinol also from phenanthrene-3-aldehyde with methylmagnesium iodide, and the 2- and 3-ethylphenanthrenes by the reduction of the ketones with amalgamated zinc according to Clemmensen. Phenanthryl-9-methylcarbinol and 9-ethylphenanthrene had been prepared by Pschorr[21] by the action of acetaldehyde on phenanthryl-9-magnesium bromide, and by reduction of the carbinol by zinc dust distillation, respectively. The identity of these compounds (the 2- and 3-derivatives directly compared) with those obtained by catalytic reduction excludes the possibility of a nuclear reduction in the latter procedure.

In Table I, Willgerodt and Albert's "9-acetylphenanthrene," 2-, 3- and 9-acetylphenanthrenes, and the compounds prepared from these ketones are presented. These data make it difficult to decide the identity of the product described by Willgerodt and Albert.

TABLE I

ACETYLPHENANTHRENES

	Willgerodt's "9-acetylphenanthrene"	-2-	-3-	-9-
Crystal form	Leaflets	Needles	Needles	Needles
Melting point, °C.	123	143	72	74.5
Semicarbazone, m. p., °C.		297–299	228–230	199–201
Oxime, m. p., °C.	80		143.5–144	154–154.5
Phenylhydrazone, m. p., °C.	181	187–188	192.5–194	
Picrate, m. p., °C.			125–125.5	107–108

PHENANTHRYLACETIC ACIDS

	Willgerodt "-9-"	-2-	-3-	-9-
Melting point, °C.	213–215	181–183	175–177	219–221

PHENANTHRYLMETHYLCARBINOLS AND ETHYLPHENANTHRENES

	Pschorr -9-	Willgerodt "-9-"	-2-	-3-	-9-
Carbinol, m. p., °C.	137	136	135–135.5	83–83.5	135.5–136
Ethylphenanthrene, m. p., °C.	61–63	61	67–68	Liquid	62.5–63
Ethylphenanthrene-picrate, m. p., °C.	124		95.5–96	121.5–122	123–124

Experimental

9-Acetylphenanthrene: $C_{14}H_9COCH_3$.—A mixture of 250 cc. of ethyl acetate, 50 g. of sodium wire and 25 g. of phenanthrene-9-carboxylic acid methyl ester in a 750-cc. round-bottomed flask was heated to continuous reflux in an oil-bath. After nine hours, in the course of which time 80 cc. more of ethyl acetate had been added, and the temperature of the bath had risen to 170°, all the sodium had disappeared. Upon cooling the reaction mixture to room temperature, the contents of the flask were taken up in water, acidified with dilute hydrochloric acid and extracted with ether. The ether extract was dried, and after removal of the ether some ethyl acetate and acetoacetic ester was distilled off in a vacuum. The oily residue, containing the keto ester $C_{14}H_9COCH_2COOC_2H_5$, which could not be crystallized by any means, was decomposed by refluxing

(21) Pschorr, *Ber.*, **39**, 3128 (1906).

for eight hours with 400 cc. of 10% sulfuric acid, the reaction mixture, cooled, and extracted with ether. The ethereal solution was extracted with a dilute potassium hydroxide solution, dried over sodium sulfate and the ether evaporated. The oily residue was heated for about ten minutes with a 40% alcoholic potassium hydroxide solution in order to decompose unchanged phenanthrene-9-carboxylic acid methyl ester, poured into water and the alcohol removed. The 9-acetylphenanthrene was taken up in ether, and the ethereal solution on evaporation gave a slightly yellow colored oil which soon crystallized. The product was distilled in an oil-pump vacuum in a sabre-flask, and the distillate recrystallized. The yield was 82.5% of the theoretical.

TABLE II

Substance	Solvent of recrystn.	M. p., °C.	Crystal form	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
9-Acetylphenanthrene[a]	CH_3OH	74–74.5	White needles	$C_{16}H_{12}O$	87.23	5.50	86.90	5.76
-Semicarbazone	CH_3OH	199–201	White plates	$C_{17}H_{15}ON_3$	N, 15.16		15.46	
-Oxime	CH_3OH	154–154.5	White needles	$C_{16}H_{13}ON$	N, 5.96		5.95	
-Picrate	CH_3OH	107–108	Yellow needles	$C_{22}H_{15}O_8N_3$	N, 9.36		9.54	

[a] Oxidation with chromic acid in glacial acetic acid (at 70–80°) yields phenanthrene-9,10-quinone of m. p. 201–204°. The mixed melting point with phenanthrene-9,10-quinone (Kahlbaum, m. p. 202–204°) was 201–204°. Oxidation with a 2% sodium hypochlorite solution gives phenanthrene-9-carboxylic acid of m. p. 250–252°. A mixed melting point with a sample of phenanthrene-9-carboxylic acid prepared from 9-bromophenanthrene [Mosettig and van de Kamp, THIS JOURNAL, **54**, 3328 (1932)] showed no depression.

Conversion of 2-, 3- and 9-Acetylphenanthrenes into the Corresponding Phenanthrylacetic Acids.—Two grams of the ketone was heated in a sealed tube with 30 cc. of yellow ammonium sulfide solution at 170° for twenty-four hours. The reaction mixture, consisting of a dark yellow solution and a crystalline cake, was worked up in the following way. The solution was decanted, diluted with water and acidified. The cake was finely powdered, extracted with ammonium sulfide in order to remove sulfur, and refluxed for six hours with a 25% methyl alcoholic potassium hydroxide solution so as to hydrolyze the amide formed in this reaction. The acid obtained from this hydrolysis, combined with that from the original solution, was further purified by several reprecipitations, and by recrystallizations from methyl alcohol.

Substance	M. p., °C.	M. p. methyl ester, °C.	
Phenanthryl-2-acetic acid	181–183	78–78.5	
Phenanthryl-3-acetic acid	175–177	Methyl ester liquid	M. p. of methyl ester picrate, 103.5–104
Phenanthryl-9-acetic acid	219–221	75–75.5	

The acids were identical with those obtained on hydrolysis of the phenanthrylmethyl cyanides[22] as was shown by the melting points and mixed melting points of the acids and their methyl esters, respectively.

Reductions of the Acetylphenanthrenes: High-Pressure Reductions[23]

Reductions with Platinum Oxide.—The 2-, 3- and 9-acetylphenanthrenes were dissolved in absolute ethyl alcohol (1 part in 20 parts) with 0.01 to 0.025 part of platinum oxide. Generally the reductions proceeded very slowly. The carbinols were obtained

(22) Mosettig and van de Kamp, THIS JOURNAL, **55**, 2995 (1933).

(23) The high-pressure reductions were carried out in an apparatus described by Adkins and Cramer, THIS JOURNAL, **52**, 4349 (1930). The catalyst used was prepared according to the directions for catalyst 30 RAC, Connor, Folkers and Adkins, *ibid.*, **54**, 1138 (1932).

TABLE III

Phenanthrene	Subs., g.	Decalin,[a] cc.	Catalyst, g.	Temp., °C.	Pressure, lbs.	Time, hrs.	Yield of carbinol, %	Yield of ethylphenanthrene, %
2-Acetyl-	22	60	1.0	100[b]	1200	7	88	5
3-Acetyl-	44	60	2.0	100	1900	4	61[c]	
9-Acetyl-	22	60	1.0	140[d]	1400	5.5	60	32

[a] Decalin, practical (Eastman Kodak) was allowed to stand over sodium for two days and was then distilled at reduced pressure, b. p. 95–96° (42 mm.). [b] In another experiment where the temperature of the reduction was kept at 180–190°, a mixture of the carbinol and a larger percentage of the 2-ethylphenanthrene was obtained. [c] Beside the carbinol, a by-product melting from 100 to 130° was obtained from which, however, no uniform product could be separated. No ethylphenanthrene could be detected in this experiment. [d] At 100° no reduction took place.

quantitatively and identified with those obtained from the high-pressure reductions by their mixed melting points.

In the reduction of the 3-acetylphenanthrene, about 10% of the not yet identified product A was obtained.

TABLE IV

	Substance	Solvent of recryst.	Crystal form
1	Phenanthryl-2-methylcarbinol	C_6H_6	White leaflets
2	Phenanthryl-3-methylcarbinol[a,c]	Ligroin, b. p. 58–70°	White needles
3	-Picrate	C_2H_5OH	Orange-red needle clusters
4	Phenanthryl-9-methylcarbinol	C_6H_6	White silky needles
5	2-Ethylphenanthrene	CH_3OH	White leaflets
6	-Picrate	C_2H_5OH	Yellow needles
7	3-Ethylphenanthrene		Colorless liquid
8	-Picrate	C_2H_5OH	Orange-red needle clusters
9	9-Ethylphenanthrene	C_6H_6 + pet. ether 40–60°	White needles
10	-Picrate	C_2H_5OH	Orange-red prisms

	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. OH	Found C	Found H	Found OH
1	135–135.5	$C_{16}H_{14}O$	86.44	6.35	7.66	86.28	6.35	6.55[b]
2	83–83.5	$C_{16}H_{14}O$	86.44	6.35	7.66	86.27	6.35	7.79[b]
3	118–119	$C_{22}H_{17}O_8N_3$	N	9.31			9.36	
4	135.5–136	$C_{16}H_{14}O$	86.44	6.35	7.66	86.32	6.40	7.38[b]
5	67–68	$C_{16}H_{14}$	93.15	6.85		92.79	7.06	
6	95.5–96	$C_{22}H_{17}O_7N_3$	N	9.66			9.77	
7		$C_{16}H_{14}$	93.15	6.85		92.98	6.63	
8	121.5–122	$C_{22}H_{17}O_7N_3$	N	9.66			9.82	
9	62.5–63	$C_{16}H_{14}$	93.15	6.85		92.81	6.79	
10	123–124	$C_{22}H_{17}O_7N_3$	N	9.66			9.88	

[a] This carbinol was also prepared by the action of methylmagnesium iodide on phenanthrene-3-aldehyde [Mosettig and van de Kamp, THIS JOURNAL, **55**, 2995 (1933)] in ethereal solution. The carbinol obtained was shown to be identical with the one obtained from the 3-acetylphenanthrene, by mixed melting point and by mixed melting point of the picrates. [b] By Zerewitinoff's method. [c] By-product A, recrystallized from benzene, melting at 109–109.5°, forms white leaflets. *Anal.* Calcd. for the carbinol, $C_{16}H_{14}O$: C, 86.44; H, 6.35. Calcd. for the pinacol, $C_{32}H_{26}O_2$: C, 86.84; H, 5.93. Found: I, C, 86.34; H, 6.41. II, C, 86.05; H, 6.39.

Clemmensen Reductions.—The Clemmensen reductions of 2- and 3-acetylphenanthrenes gave poor yields (5–10%) of the ethylphenanthrenes, complex by-products being formed. Since we needed the hydrocarbons only for comparison, no attempts have been made to increase the yield in this procedure.

Summary

1. The preparation of 9-acetylphenanthrene by Claisen's condensation of phenanthrene-9-carboxylic acid methyl ester and ethyl acetate is described.

2. A comparison of Willgerodt and Albert's so-called 9-acetylphenanthrene with 2-, 3- and 9-acetylphenanthrenes is given.

3. The reduction products (phenanthrylmethylcarbinols and ethylphenanthrenes) of 2-, 3- and 9-acetylphenanthrene, obtained by different methods, are described.

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Studies in the Phenanthrene Series. VI. ω-Aminoacetylphenanthrenes and Aminomethylphenanthrylcarbinols[1]

BY ERICH MOSETTIG AND JACOB VAN DE KAMP

For the preparation of phenanthrene derivatives with the pharmacologically interesting substituents $-COCH_2NR_2$ and $-CHOHCH_2NR_2$, the synthesis of ω-halogenated acetylphenanthrenes was undertaken. First the direct introduction of the $-COCH_2Cl-$ group into the phenanthrene nucleus with chloroacetyl chloride was attempted. The reaction runs smoothly under the conditions imposed in the acetylation of phenanthrene,[2] but the purification of the crude reaction mixture, apparently consisting only of the 2- and 3-ω-chloroacetylphenanthrenes, and the separation of the isomers offered experimental difficulties which obviously made this method practically useless. Very satisfactory results, however, were obtained by bromination of the acetylphenanthrenes in absolute ethereal solution. Thus the 2-, 3- and 9-ω-bromoacetylphenanthrenes, respectively, were obtained quantitatively, and in a very pure state.

The exchange of the ω-halogen atom with dimethylamine, diethylamine and piperidine goes smoothly, as does the catalytic reduction of the tertiary ω-amino ketones to the corresponding amino alcohols. In this way the 2-, 3- and 9-ω-dimethylamino-, -diethylamino- and -piperidinoacetylphenanthrenes and the corresponding amino alcohols were prepared for pharma-

(1) This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc., and the Rockefeller Foundation.

(2) Mosettig and van de Kamp, THIS JOURNAL, **52**, 3704 (1930).