been calculated to be 32,000 cal. in water and 39,000 cal. in alcohol.

2. The rate of the reaction of chlorobromofluoroacetate ion has been measured but not interpreted. It is influenced by hydroxide ion.

3. The dependence of the PZ factor on the energy of activation has been discussed for this type of reaction.

4. The effect of the nature of the halogens and of the solvent on the rate has been discussed.

STATE COLLEGE, PENNA. RECEIVED OCTOBER 31, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

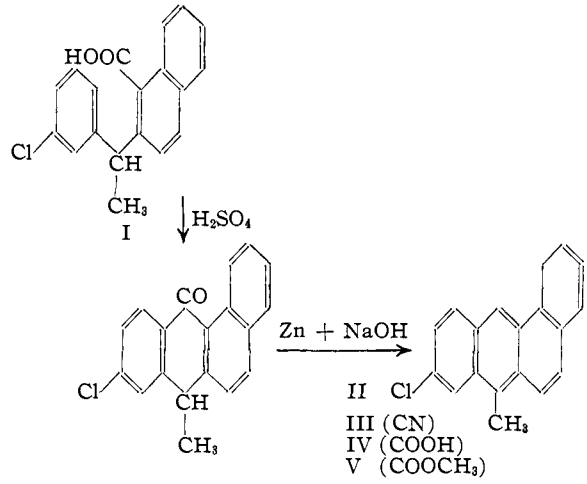
The Synthesis of 6-Chloro-10-methyl-1,2-benzanthracene and Related Compounds

BY MELVIN S. NEWMAN AND MILTON ORCHIN

As part of a coöperative study[1] on the effect of certain functional groups on the carcinogenic activity of 10-methyl-1,2-benzanthracene this Laboratory has previously reported the synthesis of 7-[2] and 5-chloro-10-methyl-1,2-benzanthracene[3] and some related compounds. The results of biological experiments[4] show that the presence of a chlorine atom in the 5- or 7-position or a cyano group in the 7-position causes considerable diminution of the carcinogenic activity of the parent compound. The amide of 5-carboxy-10-methyl-1,2-benzanthracene as well as 7-carboxy- and 7-carbomethoxy-10-methyl-1,2-benzanthracene are inactive. However, 5-cyano-10-methyl-1,2-benzanthracene rates with the parent hydrocarbon as one of the most potent sarcoma producing compounds known.[5] In view of the interesting results obtained with these variously substituted 10-methyl-1,2-benzanthracenes, we have prepared and now report the synthesis of 6-chloro-10-methyl-1,2-benzanthracene and its conversion to 6-cyano, 6-carboxy, and 6-carbomethoxy-10-methyl-1,2-benzanthracene.

The method of synthesis was entirely analogous to that employed in the preparation of the isomeric 7- and 5-substituted compounds.[2,3] The final step in the present work consisted in the cyclization of 2-(α-methyl-m-chlorobenzyl)-1-naphthoic acid, I, to the corresponding unstable anthrone and the reduction of this to 6-chloro-10-methyl-1,2-benzanthracene, II.

It was possible, but deemed unlikely, that ring closure of the acid, I, took place in the position



ortho to the chlorine atom, in which case the final compound would be the isomeric 8-chloro-10-methyl-1,2-benzanthracene. In order to establish the structure of the final compound, II, it was oxidized to a chloro-1,2-benzanthraquinone and this quinone shown to be identical with an authentic sample of 6-chloro-1,2-benzanthraquinone prepared from the known[1] 1-p-chlorobenzoyl-2-naphthoic acid, VI. The anthrone resulting from the ring closure of the crude product obtained on sodium amalgam reduction of VI was immediately reduced to 6-chloro-1,2-benzanthracene, VII. Oxidation of VII produced in good yield a quinone identical with that obtained from the oxidation of the compound produced through cyclization of 2-(α-methyl-m-chlorobenzyl)-1-naphthoic acid, I. This indicates that the compound resulting from the cyclization of I is indeed substituted in the 6-position.

All attempts[6] to cyclize the keto acid directly to the quinone, VIII, were unsuccessful. In one experiment, using a melt of aluminum chloride–

(1) All the animal experimentations were performed by Dr. M. J. Shear, whose latest summary of the results obtained appears in *Am. J. Cancer*, **33**, 499 (1938).

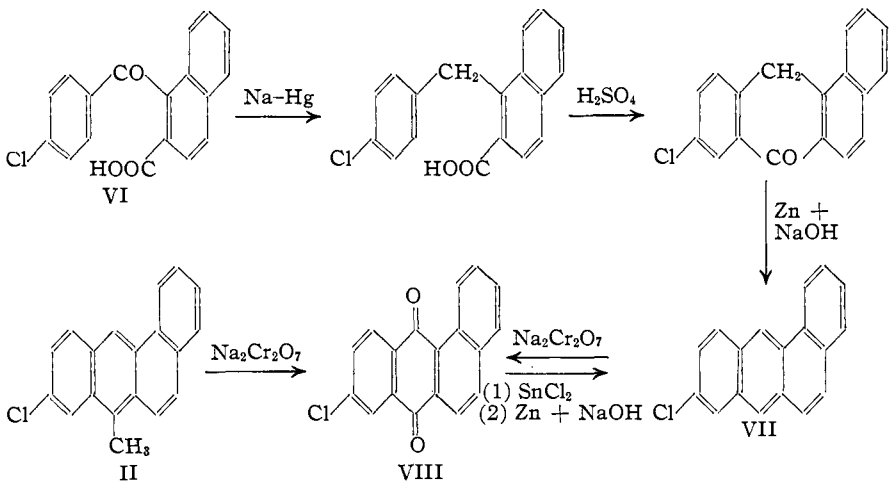
(2) Newman and Orchin, THIS JOURNAL, **60**, 586 (1938).

(3) Newman, *ibid.*, **60**, 1368 (1938).

(4) Private communication from Dr. M. J. Shear.

(5) For a complete summary of the chemistry of the cancer producing compounds see Fieser, *Am. J. Cancer*, **34**, 37 (1938).

(6) Waldmann, *J. prakt. Chem.*, **150**, 121 (1938).



sodium chloride, cyclization occurred but the only product isolated was 7-chloro-1,2-benzanthraquinone resulting from a known type of rearrangement.[7]

Experimental[8]

2-*m*-Chlorobenzoyl-1-naphthoic Acid.—To a well-stirred solution of 20.5 g. (0.104 mole) of 1,2-naphthalic anhydride in 300 cc. of benzene and 110 cc. of ether there was added all at once 90 cc. of 1.16 *M* *m*-chlorophenylmagnesium bromide. A gray colored complex formed immediately but soon changed to orange. After stirring and refluxing for three hours the mixture was decomposed with ice and hydrochloric acid and the reaction products separated into acid and neutral fractions. By fractional crystallization from acetic acid of the acid fraction there was obtained 10.1 g. (31.4%) of the more soluble 2-*m*-chlorobenzoyl-1-naphthoic acid, m. p. 186.0–189.8°. A portion recrystallized several times from acetic acid melted at 189.6–190.2°.

Anal.[9] Calcd. for $C_{18}H_{11}O_3Cl$: Cl, 11.41. Found: Cl, 11.13.

The neutral fraction on concentration yielded as a first crop 1.4 g. of unchanged starting anhydride. After extracting the mother liquor with aqueous ammonia to remove any remaining anhydride, there was obtained 3 g. of colorless needles (presumably a lactone similar to that previously encountered[2]) which, after several recrystallizations from alcohol, melted at 157.4–158.0°.

Anal. Calcd. for $C_{24}H_{14}O_2Cl_2$: Cl, 17.50. Found: Cl, 17.26.

Proof of Structure of 2-*m*-Chlorobenzoyl-1-naphthoic Acid.—This keto acid was decarboxylated[10] to produce a ketone, m. p. 142.0–142.6°, which when mixed with authentic *m*-chlorophenyl 2-naphthyl ketone, m. p. 142.2–142.8°, caused no depression in the melting point.

1-*m*-Chlorobenzoyl-2-naphthoic Acid—In addition to the 2-*m*-chlorobenzoyl-1-naphthoic acid obtained in the Grignard reaction with 1,2-naphthalic anhydride there was isolated 3.3 g. (10.3%) of the isomeric difficultly soluble 1-*m*-chlorobenzoyl-2-naphthoic acid, m. p. 251.0–254.0°. The sample for analysis melted at 253.0–253.6°.

Anal. Calcd. for $C_{18}H_{11}O_3Cl$: Cl, 11.41. Found: Cl, 11.36.

Proof of Structure of 1-*m*-Chlorobenzoyl-2-naphthoic Acid.—This keto acid was decarboxylated to produce a ketone, m. p. 84.0–85.0°, which when mixed with authentic *m*-chlorophenyl 1-naphthyl ketone caused no depression in the melting point.

***m*-Chlorophenyl 1- and 2-Naphthyl Ketones.**—These two ketones have been prepared previously by Cahn, Jones and Simonsen[11] and structures were assigned to each on the basis of the ability of the 1-naphthyl ketone to undergo the Scholl benzanthrone condensation and the ready formation of a 2,4-dinitrophenylhydrazone from the 2-naphthyl ketone. We have confirmed the conclusions regarding the structure of these ketones by their synthesis from *m*-chlorophenylmagnesium bromide and the appropriate naphthonitrile in a manner analogous to that previously reported.[2] ***m*-Chlorophenyl 2-naphthyl ketone** crystallized from ethanol in small colorless needles, m. p. 142.2–142.8°. ***m*-Chlorophenyl 1-naphthyl ketone** crystallized from ethanol in colorless needles, m. p. 86.2–87.0°.

Lactone of 2-(*m*-Chloro-α-hydroxy-α-methylbenzyl)-1-naphthoic Acid.—To a solution of 11.1 g. (0.036 mole) of 2-*m*-chlorobenzoyl-1-naphthoic acid in 200 cc. of ether and 250 cc. of benzene there was added dropwise an ethereal solution of 0.11 mole of methylmagnesium bromide. The gray precipitate which first formed turned yellow as the addition of Grignard reagent progressed. After refluxing for one and one-half hours the reaction mixture was decomposed with dilute hydrochloric acid. The neutral fraction, freed of acids by a sodium carbonate washing, deposited 8.9 g. (81%) of colorless needles, m. p. 112.4–114.8°. A portion recrystallized from alcohol for analysis melted at 113.8–114.8°.

Anal. Calcd. for $C_{19}H_{13}O_2Cl$: Cl, 11.48. Found: Cl, 11.41.

2-(*m*-Chloro-α-methylbenzyl)-1-naphthoic Acid. I.—A solution of 6.12 g. of the lactone of 2-(*m*-chloro-α-hydroxy-α-methylbenzyl)-1-naphthoic acid in 75 cc. of alcohol and 15 cc. of 55% sodium hydroxide solution was refluxed for eight hours and filtered from a small amount of insoluble material. The filtrate was diluted with hot water and about half of the alcohol distilled. The remainder was refluxed with 10 g. of activated zinc dust and an additional 25 cc. of 55% sodium hydroxide solution for twenty-three hours. The excess zinc was removed by filtration and a benzene extract of the acidified filtrate,

(7) Fieser and Peters, THIS JOURNAL, **54**, 3742 (1932).
(8) All melting points corrected unless otherwise noted.
(9) All chlorine analyses by the Parr bomb method.
(10) Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936).
(11) Cahn, Jones and Simonsen, *J. Chem. Soc.*, 444 (1933).

on concentration and dilution with petroleum ether, deposited 5.85 g. (95%) of colorless prisms, m. p. 158.8–159.8°. A portion recrystallized from benzene–petroleum ether melted at 160.0–160.6°.

Anal. Calcd. for $C_{19}H_{15}O_2Cl$: Cl, 11.41. Found: Cl, 11.41.

6-Chloro-10-methyl-1,2-benzanthracene, II.—In a small mortar 5.28 g. of the acid, I, was ground to a fine powder and divided roughly into two equal portions. Each portion was dissolved in 55 cc. of concentrated sulfuric acid at 15°. After two hours the resulting orange solutions were poured on ice. The precipitated yellow anthrone was collected rapidly, and immediately transferred to a flask containing 7.5 g. of activated zinc dust and 25 g. of sodium hydroxide in 300 cc. of water. The mixture was refluxed for twelve hours, cooled, acidified, and filtered. A benzene solution of the precipitate was treated with 4.2 g. of picric acid. On cooling 8.05 g. of deep red needles, m. p. 144.4–147.2°, was obtained. A benzene solution of the picrate was passed through a tower of activated alumina and the filtrate on concentration yielded as a first crop 3.98 g. of 6-chloro-10-methyl-1,2-benzanthracene, m. p. 157.4–158.2°. The mother liquor yielded an additional 0.25 g., m. p. 155.8–156.2°, making the total yield 84% based on the starting acid, I. After recrystallization from benzene–alcohol the portion taken for analysis melted at 157.6–158.2°.

Anal. Calcd. for $C_{19}H_{13}Cl$: Cl, 12.83. Found: Cl, 12.98.

The picrate which crystallized in deep red needles from benzene–ligroin melted at 146.8–147.2°.

Anal.[12] Calcd. for $C_{25}H_{16}O_7N_3Cl$: N, 8.31. Found: N, 8.51.

6-Cyano-10-methyl-1,2-benzanthracene, III.—One gram of II was treated with 0.68 g. of cuprous cyanide and 1–2 cc. of pyridine in precisely the manner previously described.[2] A benzene solution of the resulting nitrile, III, was passed through a tower of activated alumina and on concentration of the filtrate there was obtained as a first crop 0.68 g. (70%) of yellow prisms, m. p. 204.4–205.2°. Concentration of the mother liquor gave 0.14 g. (15%) of orange colored prisms, m. p. 202.8–204.0°. A portion recrystallized for analysis had a melting point of 204.4–205.2°.

Anal. Calcd. for $C_{20}H_{13}N$: N, 5.24. Found: N, 5.23.

6-Carboxy-10-methyl-1,2-benzanthracene, IV.—A solution of 0.50 g. of III in 50 cc. of glacial acetic acid and 10 cc. of 60% sulfuric acid was refluxed for twenty-three hours, during which time some of the very insoluble resulting acid precipitated. On cooling there was obtained 0.52 g. (96%) of yellow needles of m. p. 318–324°. Recrystallized from acetic acid, the acid melted at 328–330°, uncorr., with decomposition.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.89; H, 4.93. Found: C, 84.29; H, 5.12.

6-Carbomethoxy-10-methyl-1,2-benzanthracene, V.—To a solution of 0.235 g. of IV in 50 cc. of dioxane there was added an excess of ethereal diazomethane. After standing overnight the solution was concentrated and 0.169 g. (68.5%) of the ester, V, separated in pale yellow plates. Recrystallized from dioxane–methanol the ester melted at 146.2–147.0°.

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.97; H, 5.37. Found: C, 84.10; H, 5.55.

6-Chloro-1,2-benzanthraquinone, VIII.—A mixture of 0.4 g. of II and 0.8 g. of sodium dichromate dihydrate in 15 cc. of glacial acetic acid was refluxed for one-half hour. On cooling 0.12 g. of orange needles separated which, after recrystallization from acetic acid melted at 201.0–202.0°. A mixed melting point with an authentic sample of the 6-chloro-1,2-benzanthraquinone, prepared as described below, showed no depression.

A solution of 2.0 g. of VI in 150 cc. of water and 30 cc. of alcohol containing the calculated quantity of sodium hydroxide was treated with 2% sodium amalgam for twenty-four hours at room temperature and for fifteen hours at the temperature of the steam-bath. The solution was decanted into concentrated hydrochloric acid and warmed on the steam-bath for two hours. The organic acid fraction obtained from this mixture by the usual method formed a viscous oil.[13] This product was dissolved in concentrated sulfuric acid and after one and one-half hours at room temperature the deep orange solution was poured on cracked ice. The anthrone was collected rapidly and reduced with 3 g. of activated zinc dust and 14 g. of sodium hydroxide in 200 cc. of water. The mixture was refluxed for twelve hours, cooled, acidified, and filtered. The precipitate on crystallization from benzene deposited 0.27 g. of yellow plates, m. p. 158.8–159.0°, after softening at 153°. A solution of 0.113 g. of these yellow crystals in 10 cc. of glacial acetic acid was refluxed with 0.2 g. of sodium dichromate for ten minutes. A few drops of hot water was added and on cooling the solution deposited 0.105 g. of 6-chloro-1,2-benzanthraquinone which on recrystallization from acetic acid melted at 201.0–202.0°.

Anal. Calcd. for $C_{18}H_9O_2Cl$: Cl, 12.12. Found: Cl, 12.54.

In an attempt to prepare the quinone, VIII, directly from 1-*p*-chlorobenzoyl-2-naphthoic acid, VI, 1.0 g. of VI was added to a melt prepared from 1.2 g. of sodium chloride and 6.5 g. of aluminum chloride.[7] After heating at 160–165° with continuous stirring for thirty minutes, the tarry mass was thrown on ice. The precipitated material was collected, dried and distilled. Crystallization of the distillate from glacial acetic acid resulted in a mixture consisting of unchanged keto acid and quinone from which it was possible to separate the orange quinone crystals mechanically. The chloroanthraquinone melted at 225° and when mixed with an authentic sample of 7-chloro-1,2-benzanthraquinone[2] of m. p. 232.2–232.8° gave no depression of the melting point, indicating that the cyclization had resulted in a rearrangement.

6-Chloro-1,2-benzanthracene, VII.—For the reduction of VIII the two step method of Cook was employed.[13]

(12) Nitrogen analyses by the micro Dumas method.

(13) Cook, *J. Chem. Soc.*, 456 (1932). In this work Cook reduced the two cuminoyl naphthoic acids with zinc dust and alkali and similarly obtained non-crystalline products.

To a solution of 0.10 g. of VIII in 15 cc. of glacial acetic acid there was added a solution of 0.5 g. of stannous chloride in 5 cc. of concentrated hydrochloric acid. After refluxing for one hour the solution was diluted with water and the yellow precipitate collected and transferred to a flask containing 0.3 g. of activated zinc dust and 1 gram of sodium hydroxide in 10 cc. of water. The mixture was refluxed for three hours, cooled, filtered and the precipitate digested with hydrochloric acid to remove the excess zinc. Crystallization of the insoluble material from benzene–alcohol yielded 0.05 g. of material, m. p. 160.4–161.4°. A portion dissolved in benzene–alcohol crystallized in colorless plates, m. p. 160.6–161.8°.

Anal.[14] Calcd. for $C_{18}H_{11}Cl$: Cl, 13.50. Found: Cl, 13.75, 13.92.

Summary

The following compounds have been prepared in order to test their biological activity: 6-chloro-10-methyl-1,2-benzanthracene, 6-cyano-10-methyl-1,2-benzanthracene, 6-carboxy-10-methyl-1,2-benzanthracene, and 6-carbomethoxy-10-methyl-1,2-benzanthracene.

(14) Chlorine analysis by Dr. Tsu Sheng Ma using the catalytic combustion method.

COLUMBUS, OHIO RECEIVED NOVEMBER 30, 1938

[CONTRIBUTION FROM THE NAVAL STORES RESEARCH DIVISION, BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

The Composition of So-Called Pyroabietic Acid Prepared without Catalyst

BY E. E. FLECK AND S. PALKIN

In a previous publication[1] a method for the resolution of the so-called "pyroabietic acid" prepared by catalytic means was described. The isolation of dehydro-, dihydro- and tetrahydroabietic acids from this complex established beyond doubt the true nature of this product and confirmed the prior inferences of Fieser and Campbell,[2] based on spectroscopic data and certain nitration derivatives. Since then, these findings have been further confirmed by Ruzicka, Bacon, Sternbach and Waldmann,[3] and by Littmann.[4]

Ruzicka and associates isolated dehydroabietic acid and a dihydroabietic acid (m. p. 193–194°; $[\alpha]^{20}D$ +9°) from pyroabietic acid prepared by heating *l*-abietic acid, without catalyst, for eighty hours at 250°. These authors suggest that other dihydroabietic acids are probably present in the pyroabietic acid mixture.

Littmann, on the other hand, isolated dehydro- and tetrahydroabietic acid from a catalytically treated abietic acid.

In a subsequent paper[5] we have shown that one of the two isomeric dihydro compounds isolated was unique because of its high specific rotation $[\alpha]^{20}D$ +108°. The other dihydro compound was isolated in the form of a lactone in which the acid group lactonized on the double bond, and was identical with that reported by Ruzicka and Meyer,[6] and, more recently, by Hasselstrom, Brennan and McPherson.[7]

In preparing pyroabietic acid by heat alone it has been the practice to heat the rosin or abietic acid at a temperature of about 250° for a period of eighty to one hundred hours. La Lande[8] in his study of the effect of temperature and the length of heating period on *l*-abietic acid, showed that heating for three and one-half hours at 330° formed a product with an acid number of 100, a saponification number of 141, and a specific rotation of $[\alpha]^{20}D$ +47°. La Lande, however, was not concerned with the actual isolation of the pyroabietic acid mixture. Since the yield of this material is as good, if not better, than that obtained by the longer heating period at 250°, this more rapid method of preparing crude pyroabietic acid was used. While the properties of the so-called pyroabietic acid prepared in this manner as reported by Fanica[9] and others agreed well with those of the catalytically prepared pyroabietic acid, it was thought unlikely that the disproportionation reaction involved would be the same in the two cases.

The purpose of this work, therefore, was to prepare pyroabietic acid from pure *l*-abietic acid by heat alone and to determine in what respects this product differs from the pyroabietic mixture obtained when a catalyst, such as palladium–carbon, is used.

(1) Fleck and Palkin, THIS JOURNAL, **60**, 921 (1938).
(2) Fieser and Campbell, *ibid.*, **60**, 159 (1938).
(3) Ruzicka, Bacon, Sternbach and Waldmann, *Helv. Chim. Acta*, **21**, 591 (1938).
(4) Littmann, THIS JOURNAL, **60**, 1419 (1938).
(5) Fleck and Palkin, *ibid.*, **60**, 2621 (1938).
(6) Ruzicka and Meyer, *Helv. Chim. Acta*, **5**, 333 (1922).
(7) Hasselstrom, Brennan and McPherson, THIS JOURNAL, **60**, 1267 (1938).
(8) La Lande, Jr., *Ind. Eng. Chem.*, **26**, 679 (1934), Table 1.
(9) Fanica, *Bull. inst. pin*, 183 (1933).