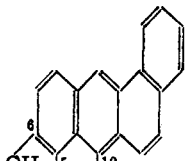
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

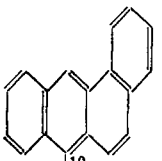
The Synthesis of 7-Chloro-10-methyl-1,2-benzanthracene and Related Compounds[1]

BY MELVIN S. NEWMAN AND MILTON ORCHIN[2]

It has been demonstrated amply that the 1,2-benzanthracene ring system is possessed of latent carcinogenic activity which may be developed to various degrees by introduction of alkyl groups at different positions. The most potent carcinogenic agent of this series is methylcholanthrene (I) which may be considered as a 1,2-benzanthracene with substituents at positions 5, 6, and 10. From the information at present available, it appears that 10-methyl-1,2-benzanthracene (II) is the only monosubstituted 1,2-benzanthracene which compares favorably with I in the rapidity and regularity of sarcoma production.[3]



I



II

In view of the striking physiological activity of II, it seemed of interest to prepare a series of 10-methyl-1,2-benzanthracenes containing various functional groups in order to test their effect on the activity of the parent compound. It was decided to attempt the synthesis of a chloro derivative. Such a compound would be of interest not only of itself but also because it would provide a starting material for the preparation of other compounds containing groups substituted in place of the chlorine atom.

The synthesis of 7-chloro-10-methyl-1,2-benzanthracene (VI) and its conversion into 7-cyano- (VII), 7-carboxy- (VIII) and 7-carbomethoxy-10-methyl-1,2-benzanthracene (IX) is herein reported. The method of synthesis represents a variation of the general method of preparation of *meso*-substituted 1,2-benzanthracenes developed by Fieser and Newman[4] and later applied by Cook[5] and by Newman[6] to the synthesis of 9-methyl-1,2-benzanthracene.

The Grignard reagent from 1-bromo-4-chlorobenzene (97% yield) was condensed with 1,2-naphthalic anhydride to produce a mixture of keto acids from which the desired 2-*p*-chlorobenzoyl-1-naphthoic acid (III) was isolated in a pure condition in 31% yield, while the isomeric 1-*p*-chlorobenzoyl-2-naphthoic acid was obtained in 10% yield. The ratio of isomers isolated was almost exactly the same as in the case of the similar reaction using phenylmagnesium bromide.[4] From the neutral portion of the reaction mixture there was isolated a small amount of a colorless halogen-containing substance, m. p. 167.4–167.8°, whose analysis was consistent with the probable structure of the lactone of 2-(*p,p'*-dichloro-α-hydroxybenzhydryl)-1-naphthoic acid.

The structure of the keto acid (III) was established by decarboxylation to a ketone, m. p. 125–126°, identical with *p*-chlorophenyl 2-naphthyl ketone synthesized from the condensation of *p*-chlorophenylmagnesium bromide with 2-naphthonitrile. The isomeric *p*-chlorophenyl 1-naphthyl ketone was prepared by a similar reaction using 1-naphthonitrile. As this ketone has to date not yet been obtained in a crystalline condition, it was analyzed and characterized as a red 2,4-dinitrophenylhydrazone, m. p. 275–276.5°, which, when mixed with the 2,4-dinitrophenylhydrazone of *p*-chlorophenyl 2-naphthyl ketone, m. p. 237–239°, melted at 213–215°. Scholl and Seer[7] and Cahn, Jones, and Simonsen[8] previously had isolated a ketone, m. p. 126–128° (2,4-dinitrophenylhydrazone, m. p. 235–237°), from the reaction mixture obtained by a Friedel–Crafts condensation of *p*-chlorobenzoyl chloride with naphthalene. These workers assigned the structure of *p*-chlorophenyl 1-naphthyl ketone to

(1) Part of the material presented in this paper was taken from the thesis of Milton Orchin submitted to the faculty of the Graduate School of The Ohio State University in partial fulfilment of the requirements for the Master of Arts degree in June, 1937.

(2) Ohio State University Scholar.

(3) It is now apparent that, depending on the method of testing employed, different degrees of cancer producing activity may be assigned to II (and also 5-methyl-1,2-benzanthracene). Thus II, when tested by the injection technique employed by Shear, *Am. J. Cancer*, **26**, 322 (1936), compares favorably with I in sarcoma production. However, if tested by the painting technique used by the English group, Bachmann, Cook, *et al.*, *Proc. Roy. Soc.* (London), **B123**, 343 (1937), II takes much longer than I to produce epitheliomas and papillomas. A more detailed account appears in an article by Fieser and Hershberg, THIS JOURNAL, **59**, 2502 (1937).

(4) Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936); see also *Science*, **83**, 558 (1936).

(5) Cook, Robinson and Goulden, *J. Chem. Soc.*, 393 (1937).

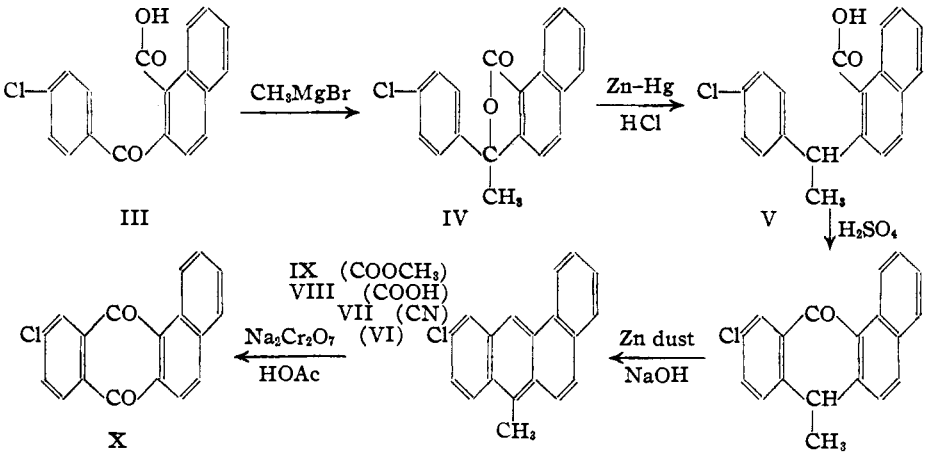
(6) Newman, THIS JOURNAL, **59**, 1003 (1937).

(7) Scholl and Seer, *Ber.*, **55**, 109 (1922).

(8) Cahn, Jones, and Simonsen, *J. Chem. Soc.*, 444 (1933).

their product on the basis of the formation of a small yield of 7-chlorobenzanthrone by fusing with sodium chloride–aluminum chloride. However, in view of the coincidence of the melting points of their ketone and its 2,4-dinitrophenylhydrazone with those of our *p*-chlorophenyl 2-naphthyl ketone, it is evident that these workers really were dealing with this isomer. We were unable to confirm the formation of 7-chlorobenzanthrone from *p*-chlorophenyl 2-naphthyl ketone but did obtain a 10% yield from the 1-naphthyl isomer.

The rest of the synthesis is indicated in the chart and offered no particular difficulties. The final compound (VI) was oxidized to 7-chloro-1,2-benzanthraquinone (X).



By heating VI with cuprous cyanide and pyridine, 7-cyano-10-methyl-1,2-benzanthracene (VII) was obtained in 80% yield. Hydrolysis to 7-carboxy-10-methyl-1,2-benzanthracene (VIII) was effected by refluxing an acetic acid solution of VII containing a small amount of 65% sulfuric acid. The methyl ester IX was prepared in dioxane solution with diazomethane. Refluxing the nitrile VII with absolute methanol and sulfuric acid for seventy-five hours merely resulted in complete recovery of unchanged starting material. The compounds VI, VII, VIII, and IX are being tested for carcinogenic activity by Dr. M. J. Shear. After four months, mice injected with VI, VII, and VIII have produced no tumors. The tests using IX have been commenced but recently.

The preparation of isomeric compounds having substituents in the 5- and 6-positions is being pursued in this Laboratory.

A recent report from Dr. Shear states that 5-cyano-10-methyl-1,2-benzanthracene, m. p. 182.8–183.2°, is about as active in sarcoma production as 10-methyl-1,2-benzanthracene (II). Accordingly the preparation of various cyano-1,2-benzanthracenes will be attempted.

Experimental[9]

2-*p*-Chlorobenzoyl-1-naphthoic Acid (III).—The filtered Grignard reagent (97% yield) from 21.1 g. (0.11 mole) of 1-bromo-4-chlorobenzene in 90 cc. of ether was added all at once to a well-stirred solution of 19.8 g. (0.1 mole) of 1,2-naphthalic anhydride in 400 cc. of thiophene-free benzene and 100 cc. of ether. An orange colored complex separated immediately. After refluxing for one hour, the mixture was decomposed with dilute hydrochloric acid and the reaction products separated into acid and neutral fractions. By allowing the crude acids to crystallize from 200 cc. of acetic acid there was obtained 8.3 g. of 2-*p*-chlorobenzoyl-1-naphthoic acid (III), m. p. 190.0–191.6°. On concentration of the mother liquors additional crystalline mixtures were obtained which, when digested with hot alcohol, left undissolved almost pure 1-*p*-chlorobenzoyl-2-naphthoic acid, m. p. 251–253°. From the portion soluble in hot alcohol was obtained an additional 1.4 g. of the desired acid, making the total yield 31%. For analysis, III was recrystallized to a melting point of 191.2–191.6°.

Anal.[9c] Calcd. for $C_{18}H_{11}O_3Cl$; C, 69.57; H, 3.57. Found: C, 69.77; H, 3.73.

There was isolated 2.9 g. (10%) of the isomeric **1-*p*-chlorobenzoyl-2-naphthoic acid**, m. p. 254.0–255.6°.

Anal.[10] Calcd. for $C_{18}H_{11}O_3Cl$: Cl, 11.41. Found: Cl, 11.44, 11.32.

On concentrating the ether-benzene solution containing the neutral reaction products, there was obtained as a first crop, 1.1 g. (5.5%) of unchanged starting anhydride and, on further concentration, crystallization, and recrystallization from alcohol, 2.33 g. of white needles (pre-

(9) All melting points corrected unless otherwise noted. Analyses marked (a) Mrs. G. M. Wellwood, Harvard University; (b) Arlington Laboratories, Arlington, Va.; (c) M. Renoll, Ohio State University.

(10) All chlorine analyses by the Parr bomb method.

sumably a naphthalide), m. p. 167.4–167.8°. The mixed melting point with 1,2-naphthalic anhydride was depressed more than 20°.

Anal.[10] Calcd. for $C_{24}H_{14}O_2Cl_2$: Cl, 17.50. Found: Cl, 17.30, 17.25.

Proof of Structure of III.—The keto acid III was decarboxylated[4] and gave in good yield a ketone, m. p. 125–126°. When mixed with authentic *p*-chlorophenyl 2-naphthyl ketone, m. p. 125–126, prepared as described below, there was no depression of the melting point.

***p*-Chlorophenyl 2-Naphthyl Ketone.**—An ethereal solution of 5.0 g. of 2-naphthonitrile, m. p. 66–67°, was added to a Grignard reagent prepared from 7.5 g. of 1-bromo-4-chlorobenzene. After four hours of refluxing, during which time a yellow crystalline complex separated, the reaction mixture was decomposed with ice and hydrochloric acid. The sparingly soluble ketimine hydrochloride was collected by filtration and hydrolyzed by boiling with water. The ketone separated in crystalline form when cooled and, on crystallization from alcohol, 7.0 g. (81%) m. p. 125–126° was obtained. A portion recrystallized for analysis melted at 125.6–126.0°.

Anal.[10] Calcd. for $C_{17}H_{11}OCl$: Cl, 13.29. Found: Cl, 13.05, 13.07.

The 2,4-dinitrophenylhydrazone was prepared by the method used by the English workers.[8] In addition to the low melting form, m. p. 237.4–238.2° (lit. 235–237°, uncorr.), described by them we also isolated a higher melting form, m. p. 260–261°. The crude 2,4-dinitrophenylhydrazone (0.76 g., m. p. 234–245°) obtained from 0.5 g. of ketone was recrystallized from 15 cc. of pyridine to which a few drops of alcohol had been added. The product which crystallized at room temperature was recrystallized until the melting point no longer changed. This form of the 2,4-dinitrophenylhydrazone crystallized in bright red plates, m. p. 260–261°.

Anal.[11] Calcd. for $C_{23}H_{15}O_4N_4Cl$: N, 12.54. Found: N, 12.24.

On standing an additional 0.13 g. of product, m. p. 245–252°, separated from the original mother liquors. This was removed by filtration and the filtrate on concentration and dilution with alcohol yielded 0.36 g., m. p. 237–239°. This was recrystallized from pyridine–alcohol to yield 0.27 g. of small red crystals, m. p. 237.4–238.2°, corresponding to the form isolated by the English workers.[8] Mixtures of the two forms started to melt at 237° and were completely melted at 251°.

***p*-Chlorophenyl 1-Naphthyl Ketone.**—For comparison *p*-chlorophenyl 1-naphthyl ketone was prepared by a method similar to the above using 1-naphthonitrile.[12] The ketone has not been crystallized and for analysis a portion boiling at 203–206° at 4 mm. was taken.

Anal.[10] Calcd. for $C_{17}H_{11}OCl$: Cl, 13.29. Found: Cl, 13.19.

The 2,4-dinitrophenylhydrazone was prepared as in the case of the corresponding 2-naphthyl ketone. It was recrystallized from pyridine and from alcohol forming small orange-red prisms, m. p. 275.4–277.0°. A mixed melting point with each form of the 2,4-dinitrophenylhydrazone of *p*-chlorophenyl 2-naphthyl ketone was depressed by more than 20°.

Anal.[11] Calcd. for $C_{23}H_{15}O_4N_4Cl$: N, 12.54. Found: N, 12.51.

The directions of Cahn, Jones, and Simonsen[8] were followed in obtaining 0.2 g. of 7-chlorobenzanthrone, m. p. 188–189, from 2.0 g. of *p*-chlorophenyl 1-naphthyl ketone.

In a similar experiment with 2.0 g. of *p*-chlorophenyl 2-naphthyl ketone, 1.3 g. of unchanged starting material was obtained and no trace of 7-chlorobenzanthrone was found.

Lactone of 2-(*p*-Chloro-α-hydroxy-α-methylbenzyl)-1-naphthoic Acid, IV.—To a solution of 9.0 g. (0.029 mole) of III in 300 cc. of thiophene-free benzene was added dropwise 34 cc. of 0.00214 *M* (0.073 mole) methylmagnesium bromide. The light yellow insoluble complex which first separated took on a darker greenish tinge after approximately one molecular equivalent of reagent had been added. Shortly after all the reagent had been added, the mixture changed to a clear orange yellow solution. After four hours refluxing, the reaction mixture was decomposed with dilute hydrochloric acid. The neutral fraction, freed of acids by a sodium carbonate washing, deposited 7.1 g. (80%) of large colorless prisms, m. p. 99–100°. For analysis a sample was recrystallized from alcohol to a melting point of 99.8–100.4°.

Anal.[10] Calcd. for $C_{19}H_{18}O_2Cl$: Cl, 11.48. Found: Cl, 11.36, 11.18.

2-(*p*-Chloro-α-methylbenzyl)-1-naphthoic Acid, V.—A solution of 4.9 g. (0.016 mole) of the lactone IV in 150 cc. of acetic acid was refluxed over zinc amalgam with the gradual addition of 350 cc. of concentrated hydrochloric acid during a period of eleven hours. At the end of this time most of the product V had separated in a crystalline condition. The reaction mixture also yielded a further quantity of acid by ether extraction. A total of 3.45 g. (70%) of acid V, m. p. 226–227°, from acetic acid was obtained.

Anal.[9a] Calcd. for $C_{19}H_{15}O_2Cl$: C, 73.43; H, 4.87. Found: C, 73.79; H, 4.91.

7-Chloro-10-methyl-1,2-benzanthracene, VI.—To 50 cc. of concentrated sulfuric acid at about 15° was added 2.63 g. of powdered acid V. By triturating and swirling for one and one-half hours all solid was dissolved, giving an orange-red solution. After standing an additional hour at about 20° the reaction mixture was poured on cracked ice. The pale yellow solid anthrone which separated was filtered on a cooled Büchner funnel, washed with ice water, and transferred rapidly to a flask containing 3 g. of zinc dust (activated with copper sulfate), 150 cc. of water, 50 cc. of 55% sodium hydroxide solution, and a few drops of amyl alcohol to prevent excessive foaming. After refluxing for eight hours the reaction mixture was diluted with 200 cc. of water.[13] The solids were collected,

(11) The authors are indebted to Dr. W. M. MacNevin for this micro Dumas analysis.

(12) For a simplified method of preparation, see Newman, THIS JOURNAL, **59**, 2472 (1937).

(13) In an alternative procedure the excess zinc was dissolved by treating the reaction mixture with an excess of hydrochloric acid and the solids collected on a filter after cooling. The product thus obtained had an orange color which could, however, be easily removed by chromatographic adsorption using activated alumina.

dried, and extracted with hot acetone. On filtration and concentration of this pale yellow extract there was obtained a first crop of 0.96 g. of VI, almost colorless plates m. p. 164.2–164.8°, and a second crop of 0.48 g., m. p. 162.6–163.4°, making a total yield of 61%. For analysis a portion recrystallized from benzene–alcohol had a melting point of 164.4–164.8°.

Anal.[9a] Calcd. for $C_{19}H_{13}Cl$: C, 82.45; H, 4.73; Cl, 12.83. Found: C, 82.21; H, 4.68; Cl, 12.52.

The picrate, deep red needles from benzene–ligroin, melted at 156.4–157.0°.[14]

Anal.[9a] Calcd. for $C_{25}H_{16}O_7N_3Cl$: N, 8.31. Found: N, 8.27.

On heating a solution of 0.1 g. of VI in 4 cc. of acetic acid with 0.2 g. of sodium dichromate dihydrate for one-half hour a good yield of 7-chloro-1,2-benzanthraquinone (X) was obtained. Recrystallized from acetic acid it formed orange-yellow needles, m. p. 232.2–232.8°.

Anal.[9a] Calcd. for $C_{18}H_9O_2Cl$: C, 73.85; H, 3.09. Found: C, 73.50; H, 3.18.

7-Cyano-10-methyl-1,2-benzanthracene, VII.—In the best experiment, 0.725 g. of VI, 0.47 g. of cuprous cyanide and 1 cc. of dry pyridine were placed in a sealed tube and heated at 255 ± 5° for fifty hours. After cooling, the contents of the tube was dissolved in warm pyridine, poured into dilute ammonia, and shaken vigorously for several minutes. The mixture was extracted with warm benzene and ether and the whole filtered to remove insoluble material which interfered with separation of the layers. The benzene layer was then washed with dilute ammonia until the blue color of the copper–ammonia complex did not appear, with water, dilute hydrochloric acid, water, and finally saturated sodium chloride solution. The ether was removed by distillation and the benzene concentrated until the remaining solution was anhydrous. At this point the dark colored solution was passed through an adsorption tower containing activated alumina. The pale yellow solution thus obtained was concentrated and on cooling there separated 0.56 g. (80%) of VII, m. p. 182–183°. For analysis a portion recrystallized from benzene–petroleum ether melted at 182.6–183.0°.

Anal.[9a] Calcd. for $C_{20}H_{13}N$: N, 5.24. Found: N, 5.46.

7-Carboxy-10-methyl-1,2-benzanthracene, VIII.—In a typical experiment, 0.20 g. of VII was dissolved in 35 cc. of acetic acid, 5 cc. of 65% sulfuric acid added, and the solution refluxed for twenty hours. The hot solution was diluted with water and the acid, VIII, crystallized in fine yellow needles. The yield was almost quantitative. For analysis the acid, recrystallized from acetic acid, melted at 346–347°, uncorr.

Anal.[9b] Calcd. for $C_{20}H_{14}O_2$: C, 83.89; H, 4.93. Found: C, 83.94; H, 5.16.

7-Carbomethoxy-10-methyl-1,2-benzanthracene, IX.—To a solution of 0.10 g. of VIII in 20 cc. of dioxane was added an excess of ethereal diazomethane. After standing overnight the solution was concentrated and the ester IX separated. On recrystallization from dioxane–methanol, 0.07 g. of pale yellow needles, m. p. 186.2–186.8°, was obtained.

Anal.[9b] Calcd. for $C_{21}H_{16}O_2$: C, 83.97; H, 5.37. Found: C, 84.07; H, 5.52.

(14) The melting (or decomposition) point of picrates is much sharper and usually higher when the melting point tube is composed of Pyrex glass.

Summary

A rather general method for the synthesis of chloro derivatives of 10-methyl-1,2-benzanthracene is illustrated by the synthesis of 7-chloro-10-methyl-1,2-benzanthracene. This method involves: reaction of *p*-chlorophenylmagnesium bromide with 1,2-naphthalic anhydride; addition of methylmagnesium bromide to the ketone group of the resulting 2-*p*-chlorobenzoyl-1-naphthoic acid; reduction of the resulting lactone to an acid; and cyclization and reduction to 7-chloro-10-methyl-1,2-benzanthracene. The conversion of this into 7-cyano-, 7-carboxy-, and 7-carbomethoxy-10-methyl-1,2-benzanthracene is also described. The last four compounds are being tested for carcinogenic activity. After four months the chloro, cyano, and carboxy compounds have produced no tumors.

It was found that *p*-chlorophenyl 2-naphthyl ketone has been confused in the literature with the isomeric *p*-chlorophenyl 1-naphthyl ketone. Evidence establishing the identity of each of these ketones is presented.

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