chloride, to Dr. Alice T. Merrill for the methyl-guloside, to Miss Edna M. Montgomery for the methyl-arabinosides and to Mr. C. G. Remsburg for carrying out some of the analyses.

Summary

The oxidation of alpha-methyl-*d*-mannopyranoside with barium hypobromite was shown[2] to produce a dibasic acid which was isolated as its crystalline strontium salt and was proved to be a derivative of diglycolic acid (D'-methoxy-D-hydroxymethyl-diglycolic acid). The same strontium salt has been prepared in yields of 65–70% through oxidation of four alpha-methyl-hexosides (alpha-methyl-*d*-mannoside, *d*-glucoside, *d*-galactoside and *d*-guloside) with periodic acid followed by oxidation of the resulting dialdehyde with bromine water kept neutral with strontium carbonate. The structure of the strontium salt, particularly the presence of the *d*-glyceric acid moiety in its molecule, proves each of the four alpha-methyl-hexosides to be of the pyranoside type, this being the first proof for alpha-methyl-*d*-guloside. Beta-methyl-*d*-glucoside produces by way of these oxidation reactions a crystalline barium salt which also has the *d*-glyceric acid grouping in its molecule; evidence is presented that this salt is barium L'-methoxy-D-hydroxymethyl-diglycolate from which follows the pyranoside structure for beta-methyl-*d*-glucoside.

The alpha forms of methyl-*d*-arabinoside (−17°) and methyl-*d*-xyloside (+154°) yield another crystalline strontium salt (strontium D'-methoxy-diglycolate) and the beta forms of these two glycosides −245 and −65°, respectively) produce strontium L'-methoxy-diglycolate, the optical antipode of the salt from the alpha forms. Since the latter two strontium salts contains the glycolic acid structure in their molecules the four parent methyl-pentosides must have the pyranoside structure. A third crystalline methyl-*d*-arabinoside (+123°) yields the strontium salt with the *d*-glyceric acid grouping (the one from the alpha-methyl-*d*-aldohexopyranosides); this new methyl-arabinoside must therefore possess the furanoside structure and the alpha configuration.

The cleavage type of oxidation, having wide application among the glycosides, thus provides a new method for the determination of ring structures and for the correlation of the configuration of carbon atom 1 of glycosides. It also affords the most direct way of correlating the configuration of the sugars with glyceric acid.

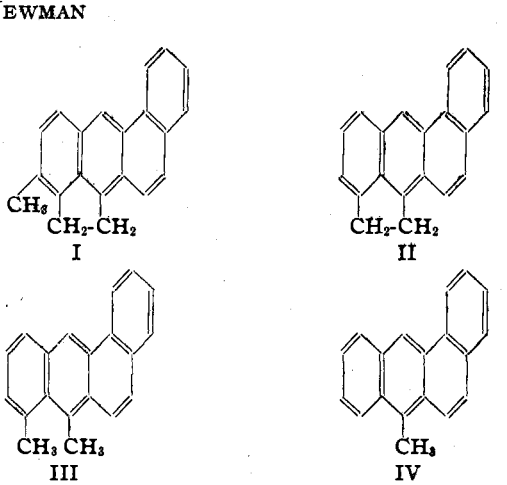
WASHINGTON, D. C. RECEIVED APRIL 5, 1937

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

The Synthesis of 1,2-Benzanthracene Derivatives Related to 3,4-Benzpyrene

BY MELVIN S. NEWMAN

In seeking to account for the carcinogenic activity of methylcholanthrene, I, and cholanthrene, II, in terms of chemical constitution,[1] Fieser and the author[2] prepared 5,10-dimethyl-1,2-benzanthracene, III, and 10-methyl-1,2-benzanthracene, IV. In that publication it was reported that III is comparable in rapidity of action to I and II. The results of further biological tests[3] indicate that IV has approximately the same activity as I, II and III. Thus, in viewing the structures of these four compounds, the conclusion is to be drawn that the structural feature necessary for strongly developed cancer-producing properties in hydrocarbons of the 1,2-benzanthracene series is substitution at position 10.



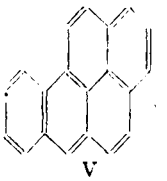
I II III IV

(1) For a more complete discussion of the carcinogenic activity of 1,2-benzanthracene derivatives see Fieser, *et al.*, *Am. J. Cancer*, **29**, 260 (1937).

(2) Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936).

(3) Private communication from Dr. M. J. Shear. See also Fieser and Hershberg, *ibid.*, **59**, 394 (1937).

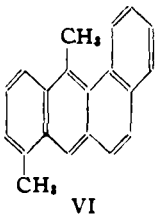
Since position 10 is a meso position, the question arises as to what effect substitution at the other meso position 9 would have. In this connection it is interesting to note that 3,4-benzpyrene, V,[4] the only known actively carcinogenic hydrocarbon which is not a 10-substituted 1,2-benz-



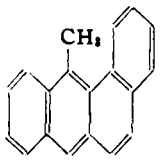
V

anthracene, may be considered as a 9-substituted derivative. Furthermore, 8,9-dimethylene-1,2-benzanthracene,[5] an isomer of II, is carcinogenic although its action is slow.[6]

In order to obtain further information concerning the effect of substitution at position 9, the preparation of 5,9-dimethyl-1,2-benzanthracene, VI, and 9-methyl-1,2-benzanthracene, VII,



VI



VII

was undertaken. In this paper the synthesis of these two hydrocarbons is reported.[7]

From the reaction of 1-naphthylmagnesium bromide with 3-methylphthalic anhydride, prepared by sulfur dehydrogenation of the addition product from piperylene and maleic anhydride[8] a mixture was obtained from which the desired keto acid, VIII, was isolated easily in 52% yield. A small amount (about 1.5%) of the isomeric 2-(1-naphthoyl)-*m*-toluic acid was also separated. The structures of the keto acids were established by decarboxylation to the known 1-naphthyl *m*-tolyl and *o*-tolyl ketones.[9]

(4) Cook, Hewett and Hieger, *J. Chem. Soc.*, 395 (1933).

(5) Fieser and Seligman, THIS JOURNAL, **57**, 2174 (1935).

(6) Shear, *Am. J. Cancer*, **28**, 334 (1936).

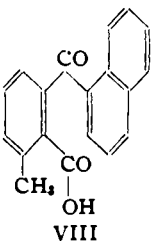
(7) The new hydrocarbons are being tested for carcinogenic activity by Dr. M. J. Shear. After approximately three and one-half months, 5,9-dimethyl-1,2-benzanthracene, VI, has produced tumors in 18 of 20 mice and appears to rank with I in rapidity of production of tumors. During the same period, 9-methyl-1,2-benzanthracene, VII, has only produced one tumor in 20 mice. While in press the synthesis of VII by Cook, *et al.*, *J. Chem. Soc.*, 393 (1937), has been reported.

(8) Diels and Alder, *Ann.*, **470**, 102 (1929); Farmer and Warren, *J. Chem. Soc.*, 3221 (1931).

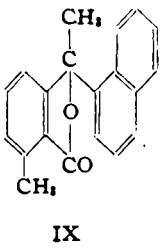
(9) Fieser and Martin, THIS JOURNAL, **58**, 1443 (1936); Bachmann, *J. Org. Chem.*, **1**, 347 (1936). Bachmann reports a melting point of 59–61° for 1-naphthyl *o*-tolyl ketone whereas Fieser and Martin, *loc. cit.*, Fieser and Newman, ref. 2, and the author give 51.5–52.5°. To clear up this discrepancy the author synthesized this ketone by Bachmann's method. The product melted at 59–61° but on crystallization of a small amount from methanol another form (thin plates) crystallized having a melting point of 51.5–52.5°. On standing for several months this sample had a melting range of 53–57°.

This ratio of isomers produced from 3-methylphthalic anhydride in the Grignard reaction stands in marked contrast to the ratio of isomers formed in the Friedel–Crafts condensation. Hayashi, *et al.*,[10] condensed 3-methylphthalic anhydride with benzene and obtained approximately 38% of 2-benzoyl-*m*-toluic acid and 10% of 6-benzoyl-*o*-toluic acid.

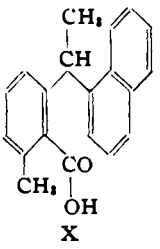
On treatment with an excess of methylmagnesium bromide, VIII was converted into the lactone, IX, in 74% yield. This lactone was reduced by zinc amalgam and hydrochloric acid in acetic acid to the acid, X, and, on cyclization with concentrated sulfuric acid at room temperature followed by reduction of the crude anthrone with zinc dust and alkali, the hydrocarbon, VI, was obtained.



VIII



IX



X

By repeating the above series of reactions using phthalic anhydride in place of 3-methylphthalic anhydride, the hydrocarbon, VII, was prepared. Of interest are the poor yields obtained in the two-step conversions of X and 2-(1-naphthylethyl)-benzoic acid into VI and VII, respectively, in contrast to the good yields in the somewhat similar preparation of III and IV.[2]

Experimental[11]

Preparation of 3-Methylphthalic Anhydride.—From the reaction between maleic anhydride and piperylene[12] was obtained 3-methyl-1,2,3,6-tetrahydrophthalic anhydride,[8] m. p. 61–62°, b. p. 155–156° at 12 mm. The observations of Farmer and Warren concerning the drop in yield of addition product when the reaction was carried out without cooling were confirmed. On dehydrogenation of 52 g. of addition product by heating at 250–260° for two hours with 20 g. (1 mol) of sulfur there was obtained, after

(10) Hayashi, Tsuruoka, Morikawa and Namikawa, *Bull. Chem. Soc. Japan*, **11**, 184 (1936).

(11) All melting points are corrected. Analyses (semi-micro) by Mrs. G. M. Wellwood, Converse Memorial Laboratory, Harvard University.

(12) The author is indebted to Drs. Dolliver, Gresham and Kistiakowsky of Harvard University for the piperylene.

vacuum distillation and crystallization from benzene–ligroin, 28 g. (54%) of sulfur-free 3-methylphthalic anhydride, m. p. 115–116°.

Synthesis of 5,9-Dimethyl-1,2-benzanthracene

6-(1-Naphthoyl)-*o*-toluic Acid, VIII.—The filtered Grignard reagent prepared from 23 g. of 1-bromonaphthalene and an excess of magnesium in 120 cc. of ether and 15 cc. of benzene[13] was added rapidly (during thirty seconds) to a well-stirred solution of 16.2 g. of 3-methylphthalic anhydride in 125 cc. of benzene. No attempt was made to condense the ether which boils off during this vigorous reaction as experience showed that when this was done, the increase in pressure was sufficient to cause mercury to splash out of the mercury-sealed stirrer. The reaction mixture was worked up as before[2] and the crude keto acids (17.8 g.) recrystallized from 65 cc. of glacial acetic acid, yielded 15.2 g. (52%) of VIII, m. p. 164–165.5°. For analysis a portion was recrystallized twice from acetic acid, the melting point rising to 165.6–166.8°.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.60; H, 4.86. Found: C, 78.44; H, 4.85.

From the original mother liquors on concentration, slow crystallization, separation of crystals by hand, and recrystallization from acetic acid, was obtained 0.45 g. (1.5%) of the isomeric 2-(1-naphthoyl)-*o*-toluic acid as fine white needles, m. p. 234–235° after sintering at 230°.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.60; H, 4.86. Found: C, 78.23; H, 5.25.

Decarboxylation of the Acids.—These reactions were carried out as before:[2] from VIII was obtained 1-naphthyl *m*-tolyl ketone, m. p. and mixed m. p. 74.5–75.8°;[9] and from 2-(1-naphthoyl)-*m*-toluic acid was obtained 1-naphthyl *o*-tolyl ketone, m. p. and mixed m. p. 51.5–52.5°.[9]

Lactone of 6-(α-Hydroxy-α-1-naphthylethyl)-*o*-toluic Acid, IX.—The filtered Grignard reagent from 1.8 g. of magnesium and methyl bromide in 90 cc. of ether was added slowly to a warm well-stirred solution of 8.7 g. of VIII in 250 cc. of benzene. The initial cream colored complex turned greenish-yellow and finally light yellow. After two hours of refluxing the mixture was decomposed with dilute hydrochloric acid. From the neutral fraction, freed of acids by a sodium carbonate washing, was obtained 6.4 g. (74%) of lactone, IX, m. p. 131.4–132.0° as white plates. A portion was recrystallized from alcohol, m. p. 131.6–132.0°.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.30; H, 5.66. Found: C, 83.07; H, 5.67.

6-(α-1-Naphthylethyl)-*o*-toluic Acid, X.—A solution of 4.74 g. of IX in 100 cc. of acetic acid was refluxed over zinc amalgam[14] for ten hours with gradual addition of 100 cc. of concentrated hydrochloric acid. The acid fraction yielded 1.9 g. (40%) of X as colorless needles, m. p. 156.0–158.5° from benzene. A portion twice crystallized from acetic acid had a melting point of 162–162.6°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.72; H, 6.25. Found: C, 82.77; H, 6.09.

5,9-Dimethyl-1,2-benzanthracene, VI.—To 20 cc. of concentrated sulfuric acid at 20° was added 1.54 g. of powdered X with swirling until a homogeneous orange solution resulted. After two hours the acid was poured on ice and the pale yellow anthrone collected by filtration. It was immediately transferred to a flask with 2 g. of zinc dust, previously activated with copper sulfate, and 100 cc. of 15% sodium hydroxide. The mixture was refluxed for five hours, a few drops of amyl alcohol being added to prevent excessive foaming. After strongly acidifying with hydrochloric acid, the product, VI, was collected on a filter and crystallized from benzene–alcohol to yield 0.50 g. of white shiny plates, m. p. 135–135.5°. In ultraviolet light the hydrocarbon has a brilliant blue fluorescence.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.70; H, 6.30. Found: C, 93.51; H, 6.57.

Synthesis of 9-Methyl-1,2-benzanthracene

Lactone of 2-(α-Hydroxy-α-1-naphthylethyl)-benzoic Acid.—The filtered Grignard reagent from 7.29 g. of magnesium and methyl bromide in 200 cc. of ether was added slowly to a warm well-stirred solution of 13.80 g. of *o*-(1-naphthoyl)-benzoic acid[15] in 200 cc. of ether and 250 cc. of benzene. The pale yellow complex which immediately separated gradually took on a greenish tinge and finally dissolved to give a pale yellow solution. After two hours of refluxing the mixture was decomposed with dilute hydrochloric acid. From the neutral fraction, freed of acids by washing with sodium carbonate, was obtained 8.0 g. (58%) of almost colorless plates, m. p. 152.8–153.6°. A sample of this compound, the desired lactone, recrystallized from alcohol melted at 154.5–155.0°.

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 83.18; H, 5.15. Found: C, 83.35; H, 5.33.

***o*-(α-1-Naphthylethyl)benzoic Acid.**—A solution of 8.6 g. of the above lactone in 150 cc. of acetic acid was refluxed over 50 g. of zinc amalgam for twelve hours with slow addition of 150 cc. of concentrated hydrochloric acid in 50 cc. of acetic acid. The mixture was diluted with water and thoroughly extracted with ether. The acid reduction product was separated by means of extraction with sodium carbonate and on crystallization from benzene–ligroin, 7.1 g. (82%) of the desired acid was obtained as white needles, m. p. 168–169°. A sample recrystallized from acetic acid melted at 169.4–170°.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.49; H, 5.89.

9-Methyl-1,2-benzanthracene.—For cyclization, 1.94 g. of the above acid was powdered and added to a cold solution of 1 g. of boric acid in 20 cc. of concentrated sulfuric acid. After two hours at room temperature the orange solution was poured on ice and the crude pale yellow anthrone reduced by boiling for six hours with 2 g. of zinc dust (activated) and 100 cc. of 12% sodium hydroxide. Amyl alcohol was again necessary to prevent foaming. After working the reaction mixture up as above there was obtained 0.45 g. (26%) of pale yellow flat needles, m. p.

(13) All benzene used in this and other Grignard reactions was thiophene free.

(14) The poor yield in this step which ordinarily (reference 2 and in this paper below) proceeds in excellent yield was probably due in this case to the poor quality of the zinc used. During the reduction the surface of the zinc had an entirely different appearance usual bright surface in such reactions.

(15) Weizmann, Bergmann and Bergmann, *J. Chem. Soc.*, 1367 (1935); Groggins and Newton, *Ind. Eng. Chem.*, **22**, 157 (1930).

138.4–138.8°. Neither the color nor the melting point was improved by chromatographic adsorption using activated alumina.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.18; H, 5.83. Found: C, 94.20; H, 5.93.

Summary

A rather general method is described for the synthesis of 1,2-benzanthracenes containing a substituent at the meso position 9. This method involves the following steps: reaction of 1-naphthylmagnesium bromide with phthalic anhydride (or 3-methylphthalic anhydride); addition of methylmagnesium bromide to the ketonic carbonyl group of the resulting keto acid; reduction of the resulting lactone to an acid; and cyclization and reduction to the hydrocarbon. In this manner, 5,9-dimethyl-1,2-benzanthracene and 9-methyl-1,2-benzanthracene have been prepared for the purpose of comparing their possible carcinogenic activity with that of 10-methyl-1,-2-benzanthracene and that of 3,4-benzpyrene.

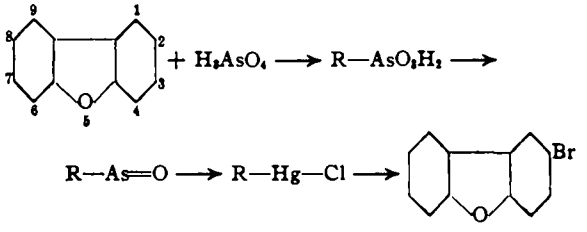
COLUMBUS, OHIO RECEIVED APRIL 3, 1937

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

Arsenicals Containing the Dibenzofuran Nucleus

BY BENJAMIN F. SKILES[1] AND CLIFF S. HAMILTON

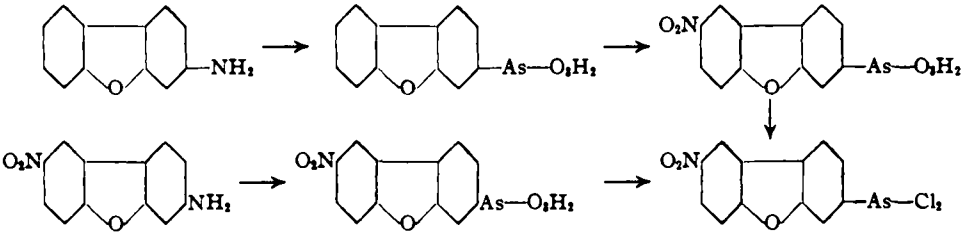
Dibenzofuran was arsonated directly by heating it with arsenic acid. The structure of the arsonic acid formed was problematical for, in the case of dibenzofuran, the nature of the entering groups has a marked effect upon the position assumed by nuclear substituents. Nitration involves principally the 3-position;[2] sulfonation,[3] and halogenation[4] favor the 2-position exclusively, while in metalation[5] the substituent enters the 4-position. The following sequence of reactions



was used to prove that dibenzofuran on direct arsonation yields 2-dibenzofurylarsonic acid.[3,6]

3-Dibenzofurylarsonic acid[7] was prepared by means of a Bart[8] reaction utilizing 3-aminodibenzofuran as a starting material. The product was nitrated to yield nitro-3-dibenzofurylarsonic acid, and then converted into nitro-3-dibenzofuryldichloroarsine which on heating to 350° with mercuric acetate gave 2-nitrodibenzofuran. This indicated that the nitro group entered either the 2- or the 8-position. Since the arsono group is a meta director in the benzene ring, and 3-nitrodibenzofuran on nitration yields 3,8-dinitrodibenzofuran, the latter structure seemed the more probable. The nitration product was shown to be 8-nitro-3-dibenzofurylarsonic acid by preparing a sample of this acid having a known structure and converting it into the dichloroarsine which was identical with the one prepared from the nitration product (mixed m. p.).

3-Dibenzofurylarsonic acid on sulfonation gave sulfo-3-dibenzofurylarsonic acid. The structure



of this compound has not been established but it is probably 8-sulfo-3-dibenzofurylarsonic acid.

(1) Parke, Davis and Company Fellow.
(2) Cullinane, *J. Chem. Soc.*, 2267 (1930).
(3) Gilman, Smith, and Oatfield, THIS JOURNAL, **56**, 1412 (1934).
(4) Mayer and Krieger, *Ber.*, **55**, 1659 (1922).
(5) Gilman and Young, THIS JOURNAL, **56**, 1415 (1934).
(6) Gilman has shown that replacement of the Hg–Cl group by bromine is reliable under the experimental conditions used in this reaction.
(7) Since the completion of this investigation, an article by Davies and Othen has appeared recording the preparation of dibenzofurylarsonic acids containing the arsono group in the 2-, 3- and 4-positions; *J. Chem. Soc.*, 1236 (1936).
(8) Bart, *Ann.*, **489**, 55 (1922).