tions, formulas IV and VIa are suggested for abietic acid and levopimaric acid, respectively.

4. Use has been made of a color test for conjugation in non-ketonic polynuclear compounds of the resin acid and sterol series. This is based upon the coupling of active dienes and trienes with *p*-nitrobenzenediazonium chloride in glacial acetic acid solution. The *p*-nitrobenzeneazo derivative of abietic acid was isolated in a crystalline condition.

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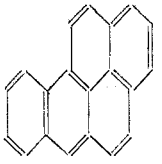
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

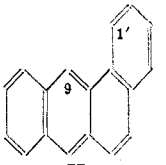
1′-Methyl- and 1′,10-Dimethyl-1,2-benzanthracene

BY LOUIS F. FIESER AND ARNOLD M. SELIGMAN[1]

Since the pentacyclic structure of 3,4-benzpyrene (I) includes the tetracyclic ring system of 1,2-benzanthracene (II), it is possible that the former hydrocarbon is properly regarded as a 1′,9-disubstitution product of the latter. For



I



II

reasons which will be discussed below, it has been assumed expressly[2] or tacitly[3] as a working hypothesis in previous publications from this Laboratory that 3,4-benzpyrene has a bond structure (I) corresponding exactly in the part of the molecule concerned to that attributed[4] to 1,2-benzanthracene (II). On this basis alkyl derivatives of 1,2-benzanthracene having suitable substituents in the 1′- and 9-positions would resemble in structure the potently carcinogenic pentacyclic hydrocarbon and might display similar physiological activity. The 1′,9-dimethyl derivative would be related to 3,4-benzpyrene in somewhat the same way that 5,10-dimethyl-1,2-benzanthracene is related to cholanthrene,[5] or that 5,6-dimethyl-1,2-benzanthracene is related to 1,2,5,6-dibenzanthracene,[6] and on the above premise a correspondence in carcinogenic activity similar to that observed in these parallel cases might be anticipated. Some features of the structure of 3,4-benzpyrene would be encountered also in the 1′- and 9-methyl, the 1′- and 9-ethyl, and the 1′,9-methylene derivatives of 1,2-benzanthracene, and all of these compounds are therefore of interest.

The synthesis of 9-methyl-1,2-benzanthracene was accomplished by Newman,[3b,7] and also by Cook, Robinson and Goulden.[8] The present paper reports the synthesis of the 1′-methyl and the 1′,10-dimethyl compounds by the application of general methods previously developed in this Laboratory.[9] *o*-(8-Methyl-2-naphthoyl)-benzoic acid (VIII), required as an intermediate in each synthesis, was prepared by condensation of the Grignard reagent from 1-methyl-7-bromonaphthalene (VII) with phthalic anhydride. The hitherto unknown naphthalene derivative VII was synthesized as shown from bromobenzene and succinic anhydride, the orientation in the Friedel and Crafts reaction being established by oxidation of III to *p*-bromobenzoic acid. The Clemmensen reduction, the cyclization to 7-bromotetralone-1 (V), the reaction of the ketone with methylmagnesium chloride, and the dehydration of the carbinol all proceeded smoothly, but some difficulty was encountered in effecting the aromatization of the dihydronaphthalene derivative VI. Dehydrogenation with sulfur or selenium was tried without success, hydrogen bromide being liberated in each instance, and the addition of bromine to the double bond and elimination of hydrogen bromide

(1) De Lamar Student Research Fellow, Harvard Medical School.

(2) Fieser, "Natural Products Related to Phenanthrene," 2nd edition, Reinhold Publishing Corp., New York, 1937, p. 84.

(3) (a) Fieser, Hershberg, Long and Newman, THIS JOURNAL, **59**, 475 (1937); (b) Fieser, Fieser, Hershberg, Newman, Seligman and Shear, *Am. J. Cancer*, **29**, 260 (1937).

(4) (a) Fieser and Lothrop, THIS JOURNAL, **58**, 749 (1936); (b) Gilman, "Organic Chemistry," John Wiley and Sons, New York, 1938, Vol. II, p. 106.

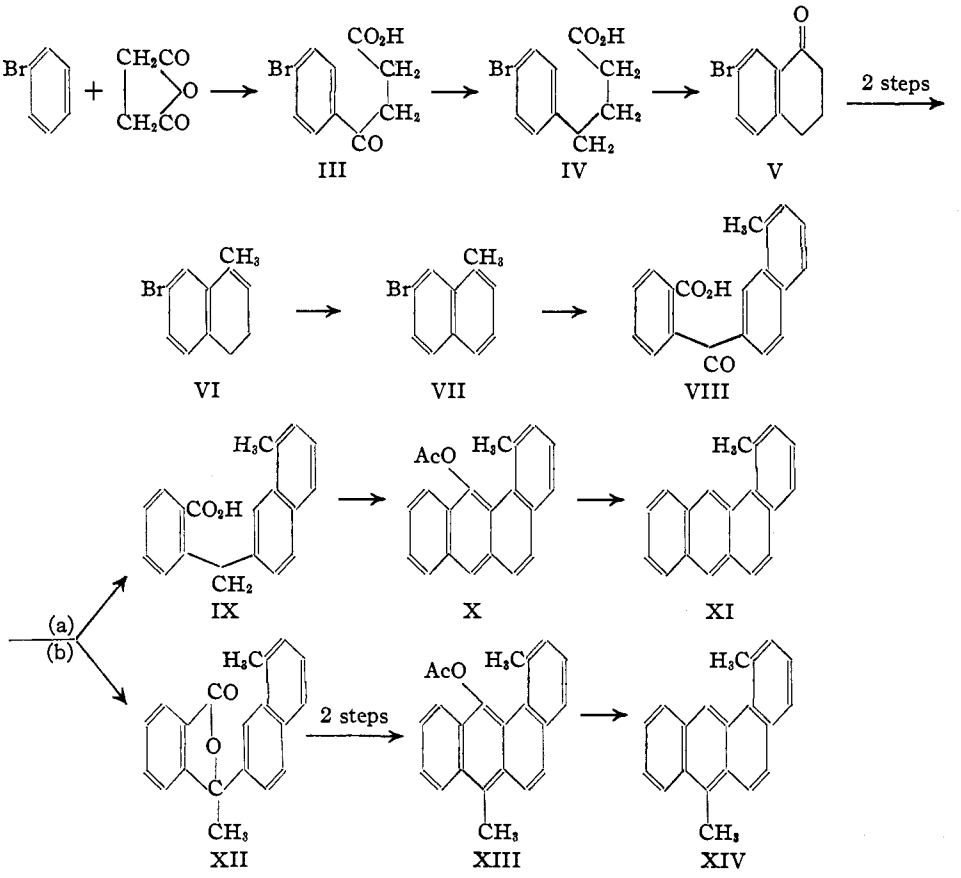
(5) Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936).

(6) Barry, Cook, Haslewood, Hewett, Hieger and Kennaway, *Proc. Roy. Soc.* (London), **B117**, 318 (1935).

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

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

(9) During a visit to the Royal Cancer Hospital in June, 1937, Professor J. W. Cook informed me that the 1′-methyl compound had been synthesized already in his laboratory. At that time work on the synthesis described in this paper was just being started, and since the method which we had selected was entirely different from that employed by the English investigators the research was undertaken as planned in order to provide material for independent bio-assay.—L. F. F.



by heating was only moderately satisfactory. The main fraction of the reaction product was an oil which appeared from the analysis to contain small amounts of higher bromination products not effectively eliminated by distillation. The material readily yielded a pure, crystalline picrate, however, and the slightly contaminated 1-methyl-7-bromonaphthalene was therefore used in the next step. A pure keto acid (VIII) was obtained without difficulty if in poor yield, and, in contrast to the behavior of 2-(α-naphthoyl)-benzoic acid,[10] the acid was reduced with zinc and alkali in excellent yield to *o*-(8-methyl-2-naphthylmethyl)-benzoic acid, IX. Cyclization under the catalytic influence of zinc chloride in acetic acid–anhydride solution[10] gave a compound having the properties of an anthranyl acetate. While ring closure conceivably can occur in either the α- or the β-position of the naphthalene nucleus, the structure X for the compound is established by the observation that the acetate can be converted into a quinone which gives the vat test. Since 1,2-benzanthraquinone forms a vat under ordinary conditions while naphthacenequinone does not,[11] the compound clearly has the angular structure. In the final step of the synthesis (a), the acetate was reduced according to Martin[12] with activated zinc dust and alkali in the presence of toluene. 1′-Methyl-1,2-benzanthracene (XI) was isolated in a colorless condition and characterized as both a mono- and a di-picrate.

An attempt to utilize 1′-methyl-1,2-benzanthranyl-10-acetate (X) for the synthesis of 1′,9-dimethyl-1,2-benzanthracene by the method of Fieser and Hershberg[10] was unsuccessful. The free anthranol, liberated from the MgBr-salt after cleavage of the acetate with *n*-butylmagnesium bromide, seems to be highly sensitive and not easily ketonized. On refluxing a solution of the substance in toluene to effect isomerization, part of the material was converted into a sparingly soluble condensation product of the type previously encountered,[10] and no addition product was obtained on interaction of the material in the filtrate with methylmagnesium chloride. In place

(10) Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).

(11) Fieser, *ibid.*, **53**, 2329 (1931).

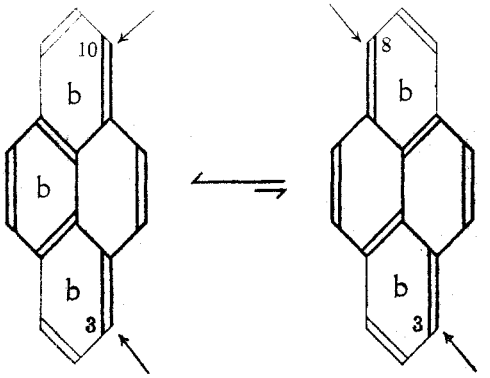
(12) Martin, *ibid.*, **58**, 1438 (1936).

of a carbinol or hydrocarbon, there was isolated a considerable amount of 1′-methyl-1,2-benzanthraquinone. This probably arises from the air-oxidation of unchanged anthranol in the course of working up the reaction mixture. An alternate synthesis of the desired dimethyl compound is now under investigation.

The isomeric 1′,10-dimethyl compound (XIV) was obtained without difficulty by applying to the intermediate keto acid VIII the synthetic operations introduced by Fieser and Newman.[5] On interaction with an excess of methylmagnesium chloride the keto acid gave a non-crystalline lactone (XII), which was reduced in good yield to a crystalline homolog of IX. This was cyclized by the catalytic zinc chloride procedure[10] to the acetate XIII, and reduction as before gave the hydrocarbon XIV. When the reaction with zinc and alkali in the presence of toluene was carried beyond a certain point, a small amount of a dihydro derivative was formed. An identical hydrocarbon was obtained by adding sodium to the dimethyl-1,2-benzanthracene (XIV) and hydrolyzing the addition product, and consequently the compound very probably is the *meso*-dihydride.

In tests conducted by one of us (A. M. S.) with Dr. M. J. Shear, 1′-methyl-1,2-benzanthracene has given no tumors or ulcers in five months, following the subcutaneous injection of the crystalline material into twenty mice. In a similar experiment the 1′,10-dimethyl compound produced severe ulceration in five mice in the first three weeks, and after 2 months no tumors had been obtained in a total of 20 survivors. From present indications 1′,10-dimethyl-1,2-benzanthracene may not rank with the 10-methyl,[5] the 5,10-dimethyl,[5] and the 5,9-dimethyl[7] compounds in potency as tested by subcutaneous injection, although it seems to be more active than the hydrocarbon having a single methyl group at the 1′-position. In the rapidity of the production of sarcomas, neither the 1′-methyl or the 9-methyl[7] compound approaches 3,4-benzpyrene as closely as 10-methyl-1,2-benzanthracene approaches cholanthrene and methylcholanthrene,[3b] but it remains to be seen whether a combination of groups in the two positions will result in an enhancement of the activity.

While this point is being investigated, we are prompted from certain theoretical considerations to explore as well another possible relationship. Hitherto we have been inclined to place some weight in the suggested analogy between 3,4-benzpyrene and 1,2-benzanthracene because of indications that the two hydrocarbons probably have similar bond structures, as expressed in formulas I and II. The structure I was favored for 3,4-benzpyrene partly because of the reported resemblance of the spectrum of the hydrocarbon to that of 1,2-benzanthracene[13] and partly because the arrangement of bonds corresponds with that tentatively preferred[14] for pyrene on the basis of early indications regarding the substitution reactions of this hydrocarbon. The previous conclusions concerning the reactions of pyrene, however, are now known to be incorrect. In a comprehensive investigation of the hydrocarbon, Vollmann, Becker, Corell and Streeck[15] recently established that pyrene is attacked by substituting agents of a variety of types chiefly in positions 3 and 10, and to a less extent at the 3 and 8 positions, while the addition of ozone occurs at the 1,2- and 6,7-positions. In our opinion these results indicate that in its most stable state pyrene has the 1,4-naphthoquinonoid[16] bond structure XV. On this view, predominant di-



XV XVI

substitution occurs at the ends of the active quinonoid system of linkages (arrows). Substitution at the 3,8-positions may occur through a possibly more reactive but much less abundant form having the 1,5-naphthoquinonoid structure XVI, the change from one form to the other involving merely a progression of the bonds in the upper terminal ring. A greater stability for XV as compared with XVI also is consistent with the Fries rule,[17] for the former structure contains

(13) Maynecord and Roe, *Proc. Roy. Soc.* (London), **A152**, 299 (1935).

(14) Ref. 2, pp. 17–18; Coulson, *J. Chem. Soc.*, 1298 (1937).

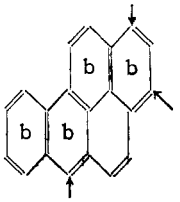
(15) Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

(16) Clar, *Ber.*, **65**, 1426 (1932).

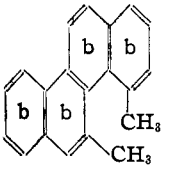
(17) Fries, Walter and Schilling, *Ann.*, **516**, 248 (1935): see also Ref. 4b, p. 92.

three benzenoid rings (b) while the latter contains but two.[18]

If pyrene has the formula XV, the most probable bond structure for 3,4-benzpyrene is that shown in formula XVII. This formulation is supported by the observation[15] that the hydrocarbon is attacked on oxidation at positions 5, 8



XVII



XVIII

and 10, and the presence of four benzenoid rings (b) would make for a structure more stable than that represented in the alternate formula I, which contains but three such rings. Since the benzenoid rings of XVII constitute a chrysene unit in the molecule, the actively carcinogenic hydrocarbon may bear a closer chemical relationship to chrysene than to 1,2-benzanthracene. In this event the physiological properties of the pentacyclic hydrocarbon might well be shared in some measure by the disubstituted chrysene XVIII. For a further understanding of the factors contributing to the carcinogenic activity of 3,4-benzpyrene it therefore appears important to examine 4,5-dimethylchrysene, together with the 4-and 5-methyl and 4,5-methylene derivatives.

Experimental Part[19]

β-(*p*-Bromobenzoyl)-propionic Acid (III).—Larsen[20] prepared this acid by the condensation of succinic anhydride with bromobenzene in the presence of one mole of aluminum chloride ($AlCl_3$) at room temperature, but under these conditions a gummy cake forms, the mixture cannot be stirred properly, and the yield is poor (50%). The same difficulty was encountered in trial experiments when the aluminum chloride was added in portions to a mixture of the other reagents, but the trouble was completely eliminated by adopting the procedure given below. The reaction does not proceed well in nitrobenzene solution.

Two hudred grams (2 moles) of finely powdered succinic anhydride was thoroughly mixed in a 5-liter flask with 540 g. (4 moles) of powdered aluminum chloride and 750 cc. of bromobenzene was added all at once. The flask was swirled to wet the solid and the mixture was heated for forty-five minutes on the steam-bath. The reaction was rapid and smooth, clouds of hydrogen chloride being evolved and the solid dissolving to a dark red solution. With the large flask employed there was no danger of frothing over. When the reaction was completed the solution was cooled well under the tap and treated cautiously with water and 540 cc. of concentrated hydrochloric acid. The excess bromobenzene was removed with volatile by-products by steam distillation and the residual acid, which solidified on cooling, was suspended in soda solution and submitted to steam distillation. The filtered solution was partially neutralized with acetic acid, clarified with Norite, and acidified. The precipitated acid was nearly colorless and melted only 8° below the purest material and it was employed directly in the next step; yield, 380 g. (74%, based on the anhydride). A sample purified by repeated crystallization from alcohol formed colorless platelets, m. p. 148–149°.

To establish the structure, 10 g. of the acid was heated with 35 g. of potassium permanganate, 5 g. of sodium hydroxide, and 500 cc. of water for several hours on the steam-bath. The excess permanganate was reduced with bisulfite and the solution was filtered and acidified. The product which separated was crystallized from dilute alcohol, giving colorless plates of *p*-bromobenzoic acid (5 g.), m. p. 251–252° (given, 250–251° uncorr.).

γ-(*p*-Bromophenyl)-butyric Acid (IV).—Following Martin's procedure,[12] reduction was accomplished by heating 225 g. of III, 600 g. of amalgamated mossy zinc, 800 cc. of concentrated hydrochloric acid, 300 cc. of water, 20 cc. of glacial acetic acid, and 400 cc. of toluene under the reflux for nine hours, with the addition of 200 cc. more acid at intervals. The toluene layer was washed, clarified, and distilled, giving 160 g. (75%) of colorless bromo acid (IV), b. p. 175–176° (3 mm.) and 20 g. of γ-phenylbutyric acid, b. p. 141–142° (3 mm.). The amount of the bromine-free acid was increased on lengthening the time of refluxing.

The acid IV crystallizes from ether–petroleum ether in colorless needles, m. p. 71–72°.

Anal. Calcd. for $C_{10}H_{11}O_2Br$: C, 49.40; H, 4.56. Found: C, 49.26; H, 4.68.

7-Bromotetralone-1 (V).—The acid IV (362 g.) was refluxed with thionyl chloride (650 cc.) for several hours and on distillation the acid chloride was obtained as a colorless liquid, b. p. 147–148° (4 mm.); yield, 320 g. (82%, 89% in a smaller run). A solution of 150 g. of this material in 200 cc. of carbon bisulfide was added during one-half hour to a stirred suspension of 90 g. of powdered aluminum chloride in 1300 cc. of carbon bisulfide at 0°, and after one hour the mixture was allowed to come to room temperature with stirring and 40 g. of aluminum chloride was

(18) The failure of 3-hydroxypyrene to couple[15] indicates a rigidity of the bond structure in at least a part of the molecule, and it appears that the attachment of a hydroxyl group at position 3 in XV represents a structure more stable than that with the substituent at position 5. The explanation may be that the hydroxyl group, which is known to have a stabilizing (potential-lowering) effect on true quinones, is joined directly to the quinonoid system in the former, but not the latter, case. In reply to an inquiry concerning 3,8- and 3,10-dihydroxypyrene, Dr. G. Krünalein kindly informed us that in tests conducted by Dr. Vollmann and co-workers neither compound could be caused to couple with diazotized *p*-nitroaniline. We interpret this observation as indicating that the dihydroxy compounds have the alternate bond structures XVI and XV, respectively. From the above reasoning, this would mean that the influence of the attachment of a hydroxyl group to a quinonoid system is so pronounced that two such groups in the 3- and 8-positions can effect the stabilization of the otherwise more reactive 1,5-naphthoquinonoid system of XVI.

(19) All melting points are corrected. Analyses by Mrs. Verna R. Keevil.

(20) Larsen, Dissertation, Harvard University, 1935.

added in portions. After refluxing for one-half hour the mixture was decomposed with ice and concentrated acid (130 cc.), the washed carbon bisulfide layer was extracted with soda to remove 1–2 g. of acid, and the product was distilled after drying and evaporating the solvent. The yield of bromotetralone, b. p. 142–143° (3 mm.), was 121 g. (94%, based on the acid chloride used). The material solidified on cooling, and a sample crystallized for analysis from ether–petroleum ether formed large, colorless prisms, m. p. 76–77°.

Anal. Calcd. for $C_{10}H_9OBr$: C, 53.34; H, 4.03. Found: C, 53.43; H, 4.06.

1-Methyl-7-bromo-3,4-dihydronaphthalene (VI).—A solution of 60 g. of V in 200 cc. of ether was added rapidly with good cooling to a stirred solution of methylmagnesium chloride prepared from 6.5 g. of magnesium in 350 cc. of ether. The mixture was then refluxed for ten minutes, cooled thoroughly, and decomposed by the careful addition of water and concentrated hydrochloric acid (100 cc.). After washing the ethereal solution with acid, soda, and water the solvent was evaporated and the residual oil was transferred to a modified Claisen flask and, after adding a boiling chip, heated in a bath at 180–190° for ten minutes to effect dehydration. After distillation at the water pump and then at a lower pressure, the product was obtained as a pale yellow liquid, b. p. 113–114° (2.5 mm.); yield, 52 g. (87%).

Anal. Calcd. for $C_{11}H_{11}Br$: C, 59.20; H, 4.97. Found: C, 59.38; H, 5.15.

1-Methyl-7-bromonaphthalene (VII).—A solution of 48 g. of the dihydro compound in 100 cc. of carbon tetrachloride was stirred at −10° and treated with 36 g. of bromine in 50 cc. of carbon tetrachloride. The bromine was added in fifteen minutes, but with vigorous stirring to keep the temperature from rising above −10°. The addition was stopped when bromine was no longer absorbed rapidly, and the solvent was then distilled. Much hydrogen bromide was evolved during the process, and after heating the oil at 200° for a few minutes to complete the process the product was distilled at the water pump from a dark resin. On fractionation there was obtained 28 g. (59%) of a pale yellow liquid, b. p. 124–125° (3 mm.), and 10 g. of material boiling at 140–141°. The composition of the main fraction indicated the presence of more highly brominated material (Calcd. for $C_{11}H_9Br$: C, 59.73; H, 4.07. Found: C, 57.61; H, 4.37), but the oil readily yielded a crystalline picrate. The higher boiling fraction contained somewhat less halogen than required for a dibromo methylnaphthalene and it yielded no picrate.

The picrate of VII crystallized from alcohol in fine yellow needles, m. p. 92.5–93.5°.

Anal. Calcd. for $C_{11}H_9Br \cdot C_6H_3O_7N_3$: N, 9.34. Found: N, 9.24.

***o*-(8-Methyl-2-naphthoyl)-benzoic Acid (VIII).**—An ethereal solution of the Grignard reagent from 28 g. of VII (purified only by distillation) and 5 g. of magnesium was evaporated to a volume of 75 cc. and diluted with 125 cc. of dry benzene. The solution was transferred under nitrogen to a dropping funnel and from this it was added as rapidly as possible with vigorous stirring to a hot (previously filtered) solution of 40 g. of phthalic anhydride in 300 cc. of benzene. A crystalline yellow complex separated at once, and after refluxing for one-half hour hydrolysis was accomplished in the usual way and the reaction product was extracted from the ether–benzene with soda solution. The acid separated on acidification as a yellow oil which slowly solidified. Crystallization from ether gave small, pale yellow prisms of a complex containing one molecule of ether; yield, 14 g. (30%). The substance softens at 118° and decomposes at 120–126° with liberation of ether.

Anal. Calcd. for $C_{19}H_{14}O_3 \cdot C_4H_{10}O$: C, 75.78; H, 6.64. Found: C, 74.80; H, 6.49.

A sample which had been powdered and dried in a vacuum oven for several hours melted at 153–153.5°.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.60; H, 4.86. Found: C, 78.67; H, 5.17.

***o*-(8-Methyl-2-naphthylmethyl)-benzoic Acid (IX).**—A mixture of 7 g. of the keto acid VIII, 12 g. of zinc dust, 20 g. of sodium hydroxide, and 200 cc. of water was refluxed for seven hours, after which it was cooled, acidified without filtration, and extracted thoroughly with ether. The washed solution was extracted with soda solution, and on acidification of the extract the product separated as a colorless oil which soon solidified. The solid was dried in ether, and on evaporation of the solvent the residue melted at 138–141° and weighed 5.2 g. (98%). A sample recrystallized from glacial acetic acid formed colorless needles, m. p. 143–144°.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.55; H, 5.84. Found: C, 82.68; H, 6.11.

1′-Methyl-1,2-benzanthranyl-9-acetate (X).—A solution of 5 g. of IX and 0.4 g. of anhydrous zinc chloride in 30 cc. of glacial acetic acid and 25 cc. of acetic anhydride was refluxed for one and one-half hours, 15 cc. of water was added very cautiously to decompose the excess anhydride, and on further dilution and cooling small yellow crystals of X were slowly deposited; yield 3.6 g. (66%). The substance forms yellow prisms from ether, m. p. 173–174°; the solution in concentrated sulfuric acid is orange in the cold and red when warmed.

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 84.00; H, 5.38. Found: C, 84.03; H, 5.64.

1′-Methyl-1,2-benzanthracene (XI).—A mixture of 2.5 g. of the acetate (X), 125 cc. of 10% sodium hydroxide solution, 8 cc. of toluene, and 12 g. of zinc dust (washed with 100 cc. of water containing 0.5 g. of copper sulfate crystals) was refluxed for seven hours. After thorough extraction of the aqueous layer and the zinc with benzene, the benzene–toluene solution was dried by partial distillation and passed through a tower of alumina. On evaporation of the filtrate and crystallization of the product from ether–petroleum ether, the hydrocarbon was obtained in the form of colorless, flat prisms or plates, m. p. 138.5–139.2°; yield, 0.85 g. (42%). The substance dissolves very slowly in concentrated sulfuric acid to a purplish solution which turns green on further heating.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.17; H, 5.83. Found: C, 94.62, 93.97; H, 6.12, 6.24.

A di-picrate was obtained from alcohol in the form of fine orange needles melting at 120–121°.

Anal. Calcd. for $C_{19}H_{14}\cdot 2C_6H_3O_7N_3$: N, 12.01. Found: N, 12.04.

On varying the concentrations, a **mono-picrate** separated from the same solvent as long red needles melting at 129.5–130.5°.

Anal. Calcd. for $C_{19}H_{14}\cdot C_6H_3O_7N_3$: N, 8.90. Found: N, 8.80.

1′-Methyl-1,2-benzanthraquinone.—As explained earlier in the paper, this quinone was isolated in the course of an attempt to synthesize 1′,9-dimethyl-1,2-benzanthracene. A solution of 3.5 g. of the anthranyl acetate X in 50 cc. of benzene was refluxed for one hour with an ethereal solution of the Grignard reagent from 5 g. of *n*-butyl bromide, and after decomposition with dilute acid the ether-benzene solution of the anthranol was washed, dried, and concentrated. Toluene was added and the solution was refluxed for one and one-half hours with the idea of effecting isomerization to the anthrone. During this period a small amount (0.2–0.4 g.) of a sparingly soluble product separated; this probably is formed as in other cases[10] by the condensation of the anthranol with the anthrone. The filtered toluene solution was treated with a solution of methylmagnesium chloride prepared from 2 g. of magnesium, which produced an orange precipitate. The reaction mixture was worked up as usual, evaporating the ether–toluene extract to dryness and passing a benzene solution of the product through a tower of alumina, but in place of a hydrocarbon there was obtained a considerable quantity (0.85 g.) of 1′-methyl-1,2-benzanthraquinone. No hydrocarbon was detected in the mother liquors.

The quinone crystallizes from benzene–ether in the form of clusters of yellow needles, m. p. 189–189.5°. The solution in concentrated sulfuric acid is green, turning to crimson on heating; the compound gives a positive vat test.

Anal. Calcd. for $C_{19}H_{12}O_2$: C, 83.81; H, 4.44. Found: C, 84.17; H, 4.67.

Synthesis of 1′,10-Dimethyl-1,2-benzanthracene

8-Methyl-2-(α-methyl-*o*-carboxybenzyl)-naphthalene.—A solution of 10 g. of *o*-(8-methyl-2-naphthoyl)-benzoic acid (VIII) in 150 cc. of ether and 50 cc. of benzene was added to a stirred solution of methylmagnesium chloride from 3 g. of magnesium and refluxing was continued for two hours. After cooling and adding dilute acid, the organic layer was washed with dilute acid, water, and sodium carbonate solution; no acidic material was extracted by the soda, indicating that the starting material had been completely consumed and that the addition product was completely lactonized. On evaporation the crude lactone XII was obtained as a viscous, pale yellow oil which failed to crystallize; yield, 9.8 g. (99%). It was consequently reduced at once.

A mixture of 9.8 g. of the crude lactone, 300 g. of amalgamated mossy zinc, 300 cc. of glacial acetic acid, 150 cc. of concentrated hydrochloric acid, and 400 cc. of water was refluxed for twelve hours, cooled, diluted, and extracted with ether. The acidic reaction product was extracted with soda and obtained on acidification as a colorless, crystalline precipitate. The material was taken up in ether, and after drying and evaporating the solvent the acid was obtained in a satisfactory condition on one crystallization from glacial acetic acid; yield, 7 g. (70%). Recrystallized from the same solvent for analysis, the acid formed clusters of small, colorless prisms, m. p. 183.5–184.5°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.75; H, 6.25. Found: C, 82.67; H, 6.41.

1′,10-Dimethyl-1,2-benzanthranyl-9-acetate (XIII).—Cyclization of the above acid (7 g.) was accomplished with zinc chloride and acetic acid–anhydride as described for the preparation of the monomethyl compound **X**, the reaction product separating directly in a crystalline and satisfactory condition; yield, 4.8 g. (63%). The substance crystallizes from ether in pale prisms, m. p. 190–191°; in sulfuric acid it gives an orange color turning deep red on heating.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.02; H, 5.77. Found: C, 84.24; H, 5.95.

1′,10-Dimethyl-1,2-benzanthracene (XIV).—The best results were obtained on refluxing for fourteen hours a mixture of the acetate XIII (1.4 g.), alkali, activated zinc dust, and toluene in the proportions specified for the preparation of XI. A longer period of refluxing led to the production of considerable of the dihydride, while unreduced acetate was recovered when a shorter time was allowed for the reaction. After extracting the aqueous layer and the zinc with benzene, the toluene–benzene solution was clarified by passage through an adsorption tower and the material collected on evaporation of the filtrate was recrystallized from alcohol; yield, 0.22 g. (19%). The purified hydrocarbon forms colorless blades melting at 122.5–123.5°, and remelting after solidification at 124–125°. The solution in sulfuric acid is red, changing on heating to violet and then purple. The **picrate** crystallizes from alcohol in crimson needles, m. p. 147–148°.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.59; H, 6.02. Picrate, calcd. for $C_{20}H_{16}\cdot C_6H_3O_7N_3$: N, 8.66. Found: N, 8.79.

9,10-Dihydro-1′,10-dimethyl-1,2-benzanthracene.—From the combined mother liquors from which the hydrocarbon XIV had been obtained there was isolated a picrate (0.1 g.) differing considerably from the picrate of XIV and consisting of fine, orange-brown needle clusters, m. p. 113–114°. In another experiment the two hydrocarbons were separated as the picrates by fractional crystallization from alcohol. The dark picrate of XIV is much less soluble than the orange-brown picrate and is easily isolated from the mixture in a pure condition. The hydrocarbon XIV recovered from the purified picrate melted no higher than the sample prepared by direct crystallization; the other hydrocarbon is not only much more soluble than XIV but tends to remain as an oil. The more soluble hydrocarbon, which proved to be the *meso*-dihydride of XIV, was recovered from the orange-brown picrate by passing a benzene solution through a tower of alumina and crystallizing the collected product from alcohol. A small amount of XIV crystallized first, and the dihydro compound then separated slowly as short, colorless needles, m. p. 108–109°. A hydrocarbon of identical melting point and mixed melting point was obtained on shaking a solution of XIV (50 mg.) in ether (5 cc.)-benzene (5 cc.) with a small piece of sodium in a closed vessel for twenty-four hours, discharging the deep purple color of the solution with a drop of alcohol, washing the solution with dilute

acid, and crystallising the material recovered from the organic layer from alcohol. The hydrocarbon dissolves slowly in sulfuric acid without the development of color. The picrate, when prepared from the pure hydrocarbon obtained from the disodium compound, crystallized from alcohol in bright orange needles, m. p. 126–127°.

Anal. Calcd. for $C_{20}H_{18}$: C, 92.98; H, 7.02. Found: C, 93.34, 92.80; H, 7.06, 7.13. Picrate, calcd. for $C_{20}H_{18}\cdot C_6H_3O_7N_3$: N, 8.62. Found: N, 8.93.

Summary

This paper reports the synthesis of the 1′-methyl and 1′,10-dimethyl derivatives of 1,2-benzanthracene from 1-methyl-7-bromonaphthalene which in turn was prepared synthetically from bromobenzene and succinic anhydride.

1′-Methyl-1,2-benzanthracene and the known 9-isomer are of interest for comparison with the actively carcinogenic 3,4-benzpyrene on the possibility that this hydrocarbon is properly regarded as a 1′,9-disubstituted 1,2-benzanthracene. From a consideration of the problem of the bond structure of 3,4-benzpyrene in the light of recent work by Vollmann, *et al.*, it is concluded that the possibility of a relationship to 4- and 5-disubstituted chrysenes also merits investigation.

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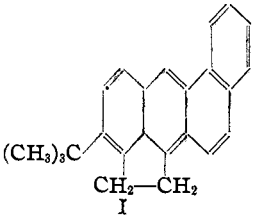
20-*t*-Butylcholanthrene

BY LOUIS F. FIESER AND DONALD K. SNOW

Among other aspects of the investigation of the relationship between carcinogenic activity and structure, it is of interest to study the variation in activity in a series of homologs related to a given cancer-producing agent of high potency. While the biological tests with the previously described[1] series of 10-alkyl-1,2-benzanthracenes are not yet complete, it has been found that the 10-ethyl homolog produces sarcomas less than half as rapidly as the 10-methyl compound when injected subcutaneously.[2] Bachmann, Cook, *et al.*,[3] have reported interesting results for 5-methyl-, 5-ethyl-, and 5-*n*-propyl-1,2-benzanthracene, all of which exert a carcinogenic action when applied to the skin. The parent hydrocarbon is practically inactive.

In the cholanthrene series the parent hydrocarbon is a highly potent carcinogenic agent and the 20-methyl derivative (sterol numbering system[4]) appears to be even slightly more active than cholanthrene.[3,5] Dr. M. J. Shear has found that 20-ethylcholanthrene (m. p. 179.5–180°, corr.), synthesized in unpublished work by Dr. W. F. Bruce of Cornell University, gives rise to tumors when injected subcutaneously but is much slower in its action than the 20-methyl compound. Tumors were produced in 8 of 16 mice in five months; a total of 11 tumors were obtained in one year, and the rest of the mice died with ulcers. The average time of the appearance of tumors (5 months) is just twice that found for 20-methylcholanthrene.[5]



I

We now report the synthesis of the higher homolog I by a process patterned closely after the first of the two methods developed by one of us with Seligman[6] for the synthesis of 20-methylcholanthrene. Most of the steps proceeded nearly as well as in the simpler case, but the yield in the final pyrolysis was considerably lower. A pure hydrocarbon was isolated without difficulty from the reaction mixture, however, and the analyses clearly indicate that the *t*-butyl group is still present and has not suffered elimination or degradation during the pyrolysis. Biological tests with the compound by Dr. Shear have been in progress for four months (injection technique), and in this time no tumors have been observed.

Experimental Part

Blanc Reaction.—The *p*-bromo-*t*-butylbenzene employed was prepared by brominating *t*-butylbenzene in the

(1) Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).
(2) Fieser and Hershberg, *ibid.*, **59**, 2502 (1937).
(3) Bachmann, Cook, Dansi, de Worms, Haslewood, Hewett and Robinson, *Proc. Roy. Soc.* (London), **B123**, 343 (1937).
(4) Fieser and Seligman, THIS JOURNAL, **57**, 1377 (1935).
(5) L. F. Fieser, M. Fieser, Hershberg, Newman, Seligman and Shear, *Am. J. Cancer*, **29**, 260 (1937).
(6) Fieser and Seligman, THIS JOURNAL, **57**, 942 (1935).