5. The action of sulfuric acid and hydrobromic acid on *n*-butyl alcohol gives no rearranged bromide.

STATE COLLEGE, PENNA. RECEIVED JULY 20, 1938

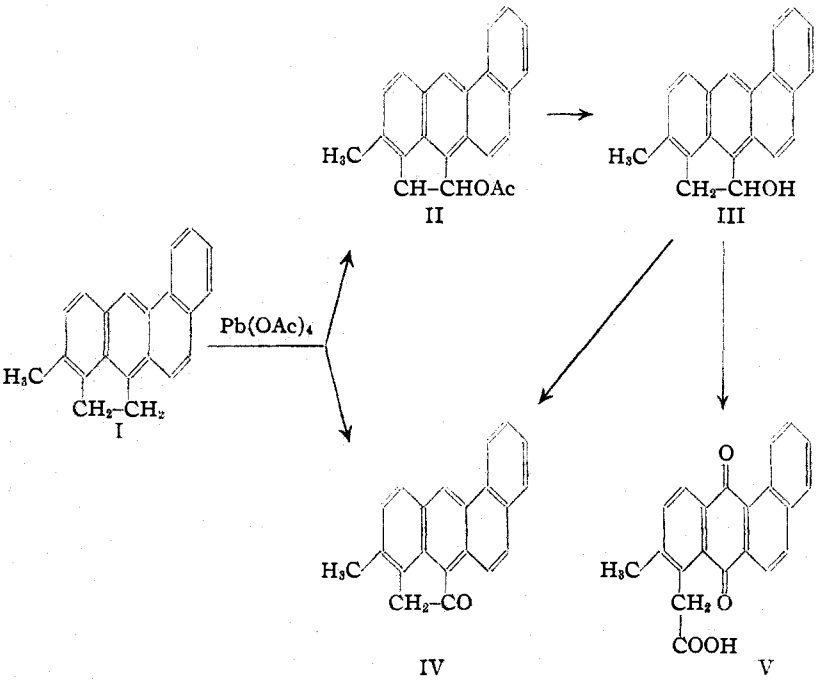
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Oxidation of Methylcholanthrene and 3,4-Benzpyrene with Lead Tetraacetate; Further Derivatives of 3,4-Benzpyrene

BY LOUIS F. FIESER AND E. B. HERSHBERG[1]

In a recent paper[2] we reported that on treatment with lead tetraacetate 1,2-benzanthracene is converted into the 10-acetoxy derivative, 10-methyl-1,2-benzanthracene is attacked in the methyl group giving 10-acetoxymethyl-1,2-benzanthracene, and 1,2,5,6-dibenzanthracene is more resistant to oxidation by the reagent and under comparable conditions is largely recovered unchanged. This specific oxidation reaction provides a means of distinguishing between hydrocarbons of varying degrees of reactivity and of locating a reactive center in a hydrocarbon molecule whether this is in an aromatic nucleus or a side chain. Thus far nuclear oxidation by the reagent has been observed only in the case of the *meso*-acetoxylation of anthracene[3] and 1,2-benzanthracene,[2] and the known examples of the oxidation of an alkyl residue by lead tetraacetate all involve acetoxylation at an activated α-position in a side chain or side ring. The reaction with 10-methyl-1,2-benzanthracene[2] is one instance of the latter type of oxidation, and similar reactions have been observed with toluene,[4] acenaphthene,[5] and tetralin.[6]

On investigating methylcholanthrene and 3,4-benzpyrene, it was found that these powerfully carcinogenic hydrocarbons are highly susceptible to attack by lead tetraacetate. 3,4-Benzpyrene is oxidized rapidly at room temperature in acetic acid–benzene and converted in over 90% yield into a new monoacetoxy derivative. Methylcholanthrene is even more susceptible to attack and in the most satisfactory procedure, adopted because of the sensitivity of the reaction products, the oxidation was conducted under ice cooling. One reaction product, isolated only in small amounts when one equivalent of oxidizing agent was employed, is a rather sparingly soluble and high melting substance having the composition of a keto derivative of methylcholanthrene. The chief product was an acetoxy derivative, and on hydrolysis it gave a neutral alcohol. A relationship between the two substances was easily established, for the alcohol was found to yield the ketone on careful oxidation with sodium dichromate. Further oxidation with the same reagent gave a yellow anthraquinone (vat test) having an acidic group, and this proved to be identical with



(1) Research Fellow on funds from the National Cancer Institute and the Eli Lilly Company.

(2) Fieser and Hershberg, THIS JOURNAL, **60**, 1893 (1938).

(3) K. H. Meyer, *Ann.*, **379**, 73 (1911).

(4) Dimroth and Schweizer, *Ber.*, **56**, 1375 (1923).

(5) Marquis, *Compt. rend.*, **182**, 1227 (1926).

(6) Criegee, *Ann.*, **481**, 263 (1930).

6-methyl-1,2-benzanthraquinone-5-acetic acid (V). Cook and Haslewood[7] obtained this acid by the oxidation of methylcholanthrene with sodium dichromate in boiling acetic acid and established the structure by decarboxylation to 5,6-dimethyl-1,2-benzanthraquinone. A comparison of our acid with a sample prepared in this way was made through the sharply melting methyl ester.[8] The alcohol and ketone therefore have the structures III and IV, the oxygen atom being located at the 15-position. Cook and Haslewood evidently had the ketone IV (m. p. 262–263°, corr.) in hand in an impure condition, for they observed that when the hydrocarbon is shaken with dichromate solution at room temperature it is changed into a substance of different crystalline form. They state that "This substance, m. p. 228–229° (dec.), probably an intermediate ketone, was not purified on account of its instability." On repeating the experiment, we found that by repeated crystallization a pure substance can be isolated and that it is identical with 15-keto-20-methylcholanthrene described above. The same ketone is therefore produced by both oxidizing agents. Whether or not the alcohol or its acetate is in each case a precursor of the ketone, the observed acetoxylation in the 15-position must be regarded as an important primary step revealing the site in the molecule most susceptible to oxidation. An oxidizing agent which introduces a hydroxyl group in a protected condition has obvious advantages for the study of primary changes.

15-Hydroxy- and 15-keto-methylcholanthrene are being tested for carcinogenic activity by Dr. M. J. Shear. The analogous alcohol, 10-hydroxymethyl-1,2-benzanthracene, has given a few subcutaneous tumors in mice[9] (slowly). Both the new alcohol, which has an asymmetric carbon atom, and the ketone present many possibilities for the preparation of additional derivatives of interest, and these are being investigated. As shown in Fig. 1, the absorption curve for 15-hydroxy-20-methylcholanthrene is very similar in form to that of the parent hydrocarbon except for a slight displacement of lower values of the extinction coefficient. The determinations, which were carried out in ether solution, using a Spekker photometer, were kindly made by Dr. George I. Lavin of the Rockefeller Institute.

Observations concerning the structure and

(7) Cook and Haslewood, *J. Chem. Soc.*, 428 (1934).
(8) Bachmann, *J. Org. Chem.*, **1**, 347 (1936).
(9) Shear, Proc. XVI Internat. Physiol. Congress, in press.

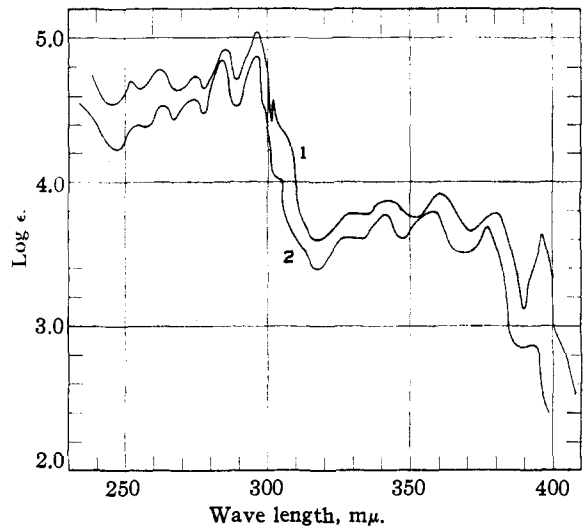
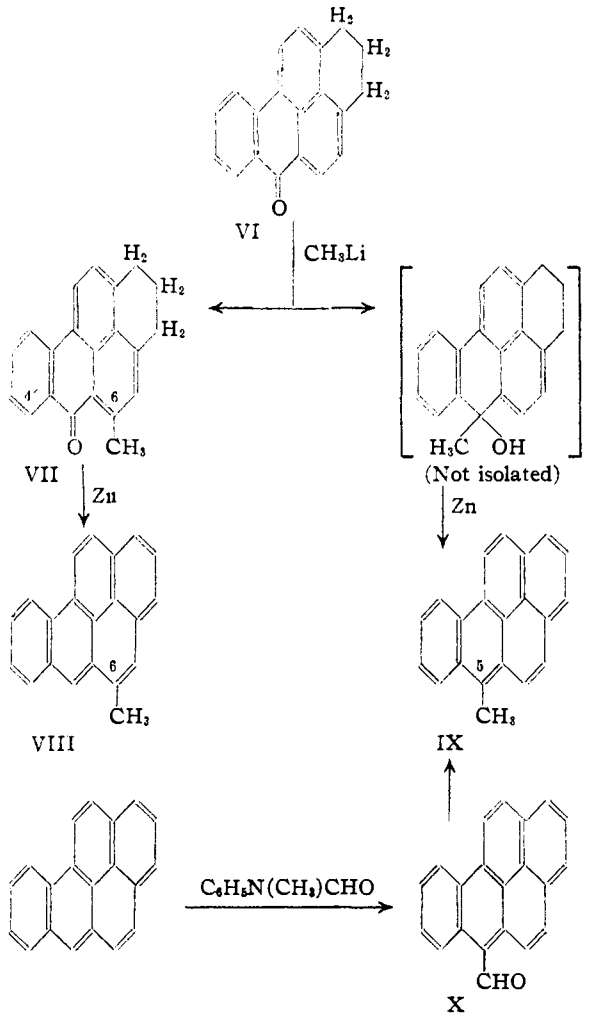


Fig. 1.—Curve 1, 20-methylcholanthrene (I); curve 2, 15-hydroxy-20-methylcholanthrene (III).

properties of the new acetoxy-3,4-benzpyrene will be reported in a later paper. Another substitution reaction studied is the condensation of the hydrocarbon with methylformanilide in the presence of phosphorus oxychloride in *o*-dichlorobenzene solution.[10] This gave in 90% yield a single, pure aldehyde, and on reduction by the Wolff-Kishner method the aldehyde yielded a methyl-3,4-benzpyrene different from any of the isomers hitherto known but identical with one of two isomers obtained synthetically from the recently described 2,1′-trimethylene-1,9-benzanthrone-10[11] (VI). It is known[12] that in the reaction of benzanthrone itself with various Grignard reagents addition may occur to the carbonyl group, giving a carbinol, and also to the 1,4-conjugated system formed by the carbonyl group and the adjacent nuclear double bond of the naphthalene nucleus. The primary product of 1,4-addition must be a dihydrobenzanthrone, but this evidently undergoes oxidation at some stage, probably in the course of working up the mixture, for the product isolated is a 4-aryl- or 4-alkyl-benzanthrone. We investigated the action of methyllithium on the trimethylenebenzanthrone VI, and from the resulting mixture isolated in 21% yield a pure, crystalline product having the composition of a methyl derivative of the trimethylenebenzanthrone. The analysis shows that the substance is

(10) Procedure of Vollmann, *et al.*, *Ann.*, **531**, 1 (1937); see also Ref. 15.
(11) Fieser and Hershberg, THIS JOURNAL, **60**, 1658 (1938).
(12) Charrier and Ghigi, *Gass. chim. ital.*, **62**, 928 (1932); *Ber.*, **69**, 2211 (1936); Allen and Overbaugh, THIS JOURNAL, **57**, 740, 1322 (1935).



a product of addition to a conjugated system rather than to the carbonyl group, and in analogy with benzanthrone the probable structure is that of formula VII. It is perhaps conceivable that 1,4-addition occurs to the alternate conjugated system and that the methyl group is at the 4'-position, but this possibility is eliminated by the observation that the hydrocarbon obtained on zinc dust distillation is quite different from the known 4'-methyl-3,4-benzpyrene.[13] The new hydrocarbon therefore can be regarded with reasonable confidence as 6-methyl-3,4-benzpyrene (VIII). After careful removal of the crystalline product from the reaction with methyllithium, zinc dust distillation of the residual oil gave, after purification through the trinitrobenzene derivative, another methylbenzpyrene. This must have come from a carbinol, although in the small-scale experiment the intermediate was not isolated, and the position of the methyl group probably corresponds with that of the carbonyl group of the starting material. A certain assurance is provided by the fact that the final hydrocarbon differs from the 2'-,[11] 3'-,[11] 4'-[13] and 6-isomers, and the substance therefore is regarded as 5-methyl-3,4-benzpyrene (IX). That the same hydrocarbon was obtained from the aldehyde indicates, at least provisionally, that this has the structure X and that in the reaction with methylformanilide 3,4-benzpyrene is substituted at the 5-position. The compounds are being tested for carcinogenic properties by Dr. Shear.[14]

The smooth reaction of 3,4-benzpyrene with methylformanilide illustrates the susceptibility of the hydrocarbon to substitution but provides little distinction in reactivity between this hydrocarbon and pyrene,[10] anthracene,[15] and 1,2-benzanthracene,[15] which also give aldehydes in good yield under comparable conditions. From the present knowledge of the condensation one can say only that 3,4-benzpyrene is more reactive to the reagent than 1,2,5,6-dibenzanthracene, which gives no aldehyde even under forcing conditions,[15] and perhaps that it is also more reactive than 1,2-benzanthracene.[15] In the oxidation experiments with lead tetraacetate 3,4-benzpyrene and methylcholanthrene appear, from qualitative observations of the temperature at which reaction occurs and from the yields, to be distinctly more reactive than any of the hydrocarbons just mentioned or than 10-methyl-1,2-benzanthracene. Both the aldehyde reaction and the oxidation are substitutions, as is the recently reported diazo coupling.[16] The color reaction with benzenediazonium chloride provides a highly sensitive and selective means of recognizing hydrocarbons of particularly highly developed reactivity, and in this test 3,4-benzpyrene and methylcholanthrene stand out in sharp contrast to 1,2-benzanthracene, 10-methyl-1,2-benzanthracene, anthracene, pyrene and in fact to all other polynuclear hydrocarbons examined except those which, like methylcholanthrene, contain an aceanthrene nu-

(13) Fieser and Fieser, THIS JOURNAL, **57**, 782 (1935).

(14) From 36 strain A mice given a subcutaneous injection of 10 mg. of crystalline 4'-methyl-3,4-benzpyrene,[13] Dr. Shear obtained 17 tumors, and the average induction time was 28 weeks. At the same dosage, 4'-methyl-1',2'-dihydro-3,4-benzpyrene[13] gave 5 tumors in 27 strain A mice in an average induction time of 34 weeks. That Domagk, *Med. Chem.*, **3**, 274 (1936), found the compound inactive in a skin painting experiment may mean either that the hydrocarbon belongs to the type much more active to subcutaneous tissue than to the skin or that aromatization occurs in contact with one tissue but not the other.

(15) Fieser and Hartwell, THIS JOURNAL, **60**, 2555 (1938).

(16) Fieser and Campbell, *ibid.*, **60**, 1142 (1938).

cleus. At the time of observing the diazo coupling of methylcholanthrene, the obvious assumption in the absence of evidence was that substitution occurs in the nucleus, probably at the available meso position, but this assumption seems questionable in the light of information which has accumulated in the meantime. The corresponding meso position of 1,2,5,6-dibenzanthracene and of 10-methyl-1,2-benzanthracene is now known to be highly hindered and not readily amenable to substitution,[2,15] and there is little reason to suppose that coupling can occur at other nuclear positions. The lead tetraacetate reaction, however, discloses the fact that a methyl or methylene group attached to the 10-meso position of the 1,2-benzanthracene nucleus constitutes a highly reactive center, and the possibility that diazo coupling occurs at the methylene group of the cholanthrenes merits consideration. The greater reactivity of hydrocarbons having in this position the methylene group of a five-membered ring, as compared with the corresponding methyl compounds, is understandable on the basis of this hypothesis, and a ready explanation is at hand of the common property exhibited by all of the hydrocarbons derived from aceanthrene.

It was pointed out previously[16] that methylcholanthrene is rather sluggish, as compared to structurally related hydrocarbons, in the addition reaction with maleic anhydride[17] and in the catalyzed addition of hydrogen.[18] According to a personal communication from Dr. W. E. Bachmann, 3,4-benzypyrene, if able to add maleic anhydride at all, at least does so far less readily than anthracene and 1,2-benzanthracene. High reactivity, however, is displayed by both of these potent carcinogens in three substitutions of entirely different types. It is important to know how various hydrocarbons compare in the relative degree of susceptibility to substitution, and an approximate estimate can be made from present data on the assumption that all three of the observed reactions are manifestations of the same kind of reactivity. The aldehyde reaction is the least selective of the tests and shows little that is not recognized from other results. The oxidation experiments reveal the course of a typical substitution and indicate that 10-methyl-1,2-benzanthracene reacts in the same way as methylcholanthrene but does so somewhat less readily. The diazo coupling tests emphasize this difference in reactivity, for the pentacyclic hydrocarbon couples and the tetracyclic compound does not. From the results of oxidation it appears that in the highly selective coupling test a moderate difference in the degree of reactivity is considerably magnified. In view of the response of the 10-methyl compound to one reagent, its failure to respond to another reagent under certain restricted conditions can no longer be taken as an indication that it lacks appreciable susceptibility to substitution.

The special significance of these observations is that there are certain points of correspondence between the chemical reactivity of the hydrocarbons in substitutions and their carcinogenic activity. The order of chemical reactivity indicated by the above tests is: methylcholanthrene and 3,4-benzyprene > 10-methyl-1,2-benzanthracene and 5,10-dimethyl-1,2-benzanthracene > 1,2,5,6-dibenzanthracene. The order of carcinogenic potency, as judged by all available criteria, is exactly the same.[19] The biological tests of simpler models of the methylcholanthrene molecule investigated in this Laboratory and of various other alkyl derivatives of 1,2-benzanthracene synthesized in London and at Harvard have brought out the importance, to the development of carcinogenic properties, of the presence of a methyl or methylene group attached to a meso carbon atom of the parent hydrocarbon, particularly at position 10; the course of the oxidation of methylcholanthrene shows that the side chain attached to the meso position 10 is the most reactive center in the molecule.[20] The superior biological potency of the cholanthrenes as compared with simpler model compounds is reflected in the distinctly higher chemical reactivity of the hydrocarbons containing the five-membered ring. Perhaps the most striking circumstance is that outstanding chemical reactivity of a special kind is encountered in the two compounds which surpass all other known hydrocarbons in the rapidity, as well as regularity, with which they induce tumors in various species and tissues of test animals. It is remarkable that substances of such distinctly different structural types as methylcholanthrene

(17) Bachmann and Kloetzel, THIS JOURNAL, 60, 481 (1938).

(18) Fieser and Hershberg, *ibid.*, 59, 2502 (1937).

(19) For a review and analysis of the biological and chemical data on hydrocarbon carcinogenesis, see Fieser, *Am. J. Cancer*, 34, 37 (1938).

(20) The reactivity manifested at this position is probably attributable to activation by the highly unsaturated center at the end of the quinonoid system of linkages, contrasting with the weaker activating influence on the alternate methylene group exerted by the terminal benzenoid ring.

and 3,4-benzypyrene both belong to the very small group of hydrocarbons capable of coupling rapidly with diazotized *p*-nitroaniline and that they show similar susceptibility to oxidation with lead tetraacetate, even though substitution occurs in one case in the nucleus and in the other in a side chain. That these unusual substances are also endowed to a high degree with the specific ability to initiate malignant growth in animal tissue may not be a mere coincidence. The relationships now observable suggest that the administered carcinogen may undergo some form of substitution reaction, possibly akin to a hydroxylation, and that this constitutes an important step in a complicated chain of events leading eventually to carcinogenesis.[21]

Experimental Part[22]

Oxidation of Methylcholanthrene.—A solution of 3.4 g. of lead tetraacetate in 100 cc. of glacial acetic acid was added dropwise in the course of one hour to a mechanically stirred solution of 2 g. of methylcholanthrene in 200 cc. of benzene, while cooling the reaction mixture with an ice-bath. The solution gradually turned deep orange during the period of the addition and when this had been completed the volume was reduced to about one-third the original by concentration at a pressure of 15–20 mm. and a temperature below 40°. Water was added and the precipitated solid was collected, washed with water, and dried in vacuum at 50°. The product was taken into acetone and after treatment with decolorizing carbon the solution was concentrated to a volume of about 100 cc. and allowed to stand overnight. The crystallizate amounted to 0.14 g. (7%) and consisted of crude **15-keto-20-methylcholanthrene (IV)**, m. p. 230–245°. Three crystallizations from acetone and one from glacial acetic acid gave yellow needles melting constantly at 262–263°. The substance is insoluble in alkali and does not give a vat test.

Anal. Calcd. for $C_{21}H_{14}O$: C, 89.34; H, 5.00. Found: C, 89.18; H, 4.89.

The acetone mother liquors remaining after the removal of the ketone were concentrated and twice treated with ligroin (60–70°) and evaporated. The acetone–ligroin solution then deposited 0.88 g. of **15-acetoxy-20-methylcholanthrene (II)**, m. p. 172–174°, dec., which when recrystallized afforded 0.78 g. of material, m. p. 177.5–178.5°, dec. From the mother liquors there was obtained 0.34 g. of acetate, m. p. 175–177°, dec., making a total yield of 46%. After three crystallizations from acetone–ligroin the acetate formed pale yellow needles melting constantly at 179.5–180.5°, with gas evolution.

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.62; H, 5.59. Found: C, 84.50; H, 5.45.

On using two moles of lead tetraacetate the yield of ketone was increased slightly but the acetate was gummy and more difficult to purify.

15-Hydroxy-20-methylcholanthrene (III).—A suspension of 0.5 g. of acetoxymethylcholanthrene in 100 cc. of methanol containing 0.5 g. of potassium hydroxide was refluxed on the steam-bath. The solid dissolved rapidly and after about twenty minutes needles of the free alcohol began to form. After one hour the mixture was cooled and the solid collected, washed with dilute methanol, dilute acid, and water. Dried in vacuum, the solid weighed 0.31 g. (71%) and melted at 207–209° with decomposition (gas evolution). Two crystallizations from acetone–ligroin gave fluffy, very pale yellow needles, m. p. 209–211°, dec.

In another experiment 0.85 g. of the acetate gave 0.55 g. (74%) of alcohol which, after one crystallization from acetone–ligroin, melted at 221–222° without gas evolution. After a second crystallization, however, the material melted at 211–213° with gas evolution, and after a third crystallization the nearly colorless substance melted at 214–216°, dec. This variable behavior is probably due to a pronounced tendency to decompose under the influence of traces of catalyst.

Anal. Calcd. for $C_{21}H_{16}O$: C, 88.71; H, 5.67. Found (214–216° sample): C, 88.41; H, 5.77.

Conversion of the Alcohol into the Ketone.—A solution of 0.19 g. of 15-hydroxy-20-methylcholanthrene in 10 cc. of glacial acetic acid was treated with 90 mg. of anhydrous sodium dichromate and shaken at room temperature for fifteen minutes. The solution was diluted with water and the precipitated ketone was crystallized from acetone. There was obtained 85 mg. (43%) of 15-keto-20-methylcholanthrene in the form of yellow needles, m. p. 262.5–263°. This did not depress the melting point of the above sample.

Dichromate Oxidation of Methylcholanthrene to the Ketone.—A suspension of 0.5 g. of powdered methylcholanthrene and 0.98 g. of anhydrous sodium dichromate in 25 cc. of glacial acetic acid was shaken at room temperature for fifteen minutes and the solid was collected, extracted with warm dilute sodium carbonate solution, and crystallized from acetone. The purification is not easy, but after five crystallizations 70 mg. (13%) of satisfactory ketone was obtained melting at 261.5–262.5°. This gave no depression when mixed with the material obtained by oxidation with lead tetraacetate.

Proof of Structure.—A solution of 0.1 g. of 15-hydroxy-20-methylcholanthrene and 0.5 g. of anhydrous sodium dichromate in 10 cc. of glacial acetic acid was refluxed for ten minutes and water was added. On recrystallization of the precipitate from acetic acid **6-methylanthraquinone-5-acetic acid** was obtained as fluffy yellow needles, m. p. 292–295°, dec.; yield, 45 mg. (39%). The substance gives a vat test and is soluble in dilute sodium carbonate solution. The **methyl ester**, obtained by esterification with methanol and hydrogen chloride, melted initially at 220.5–221.5°, and on recrystallization from benzene–ligroin formed flat yellow needles, m. p. 221.5–222°. A sample prepared by oxidation of methylcholanthrene according to Cook and Haslewood[7] and esterified as above melted at the same temperature and there was no depression on mixing the samples. Bachmann[8] esterified the quinone-acid with diazomethane in xylene and reports the m. p. 213–214°, uncorr.

Oxidation of 3,4-Benzpyrene.—A solution of 4.5 g. of lead tetraacetate in 125 cc. of glacial acetic acid was added

(21) For a further discussion of this hypothesis see Ref. 19.

(22) All melting points are corrected. Analyses by the Arlington Laboratories.

to a solution of 2.5 g. of 3,4-benzpyrene in 100 cc. of benzene, both solutions being at room temperature. After standing for one-half hour the benzene was removed by distillation and water was added to saturation. On cooling, 2.78 g. (94%) of greenish-yellow needles separated, m. p. 205.5–207.5°. Recrystallization from glacial acetic acid gave 2.5 g. (85%) of material of m. p. 208.5–209.5°, and repeated crystallization from glacial acetic acid and finally from benzene gave straw-yellow needles, m. p. 209.5–210°. The crystals from acetic acid hold this solvent tenaciously and satisfactory analytical results were obtained only after final crystallization from benzene.

Anal. Calcd. for $C_{22}H_{14}O_2$: C, 85.14; H, 4.55. Found: C, 85.33; H, 4.67.

Reaction of 2,1′-Trimethylene-1,9-benzanthrone-10 (VI) with Methyllithium.—A suspension of methyllithium was prepared from 0.5 g. of lithium and excess methyl chloride in ether and 4.85 g. of the benzanthrone VI was added. The ether was displaced by benzene, and after refluxing for fifteen hours the deep brownish-green solution was decomposed with dilute hydrochloric acid. The benzene layer was separated, washed, filtered and concentrated; it yielded two crops of crystalline product amounting to 1.06 g. (21%) and melting at 217–219°. This substance, regarded as **4-methyl-2,1′-trimethylene-1,9-benzanthrone-10 (VII)**, on further crystallization from benzene–ligroin formed golden-yellow needles, m. p. 220–220.5°.

Anal. Calcd. for $C_{21}H_{16}O$: C, 88.71; H, 5.67. Found: C, 88.67; H, 5.80.

6-Methyl-3,4-benzpyrene.—The ketone VII (0.65 g.) was mixed with 50 cc. of zinc dust and distilled at 250 mm. pressure. The oily product was redistilled at 0.5 mm. and crystallized from ether–alcohol, giving 0.27 g. (44%) of crude hydrocarbon, m. p. 154–156°. After filtering a solution of the material in benzene–ligroin through a tower of alumina, two crystallizations from benzene–ligroin gave light yellow needles, m. p. 171–171.5° (0.11 g.).

Anal. Calcd. for $C_{21}H_{14}$: C, 94.70; H, 5.30. Found: C, 94.47; H, 5.37.

The **picrate** formed silky bronze colored needles from benzene–ligroin and melted at 181.5–182.5°.

Anal. Calcd. for $C_{21}H_{14}\cdot C_6H_3O_7N_3$: N, 8.48. Found: N, 8.34.

The **trinitrobenzene derivative** crystallized as brilliant red needles from benzene-ligroin, m. p. 209–210°.

Anal. Calcd. for $C_{21}H_{14}\cdot C_6H_3O_6N_3$: N, 8.77. Found: N, 8.73.

5-Methyl-3,4-benzpyrene.—The liquors remaining from the methyllithium reaction after removal of the ketone VII were evaporated and the oily residue was distilled with zinc dust as above. On vacuum distillation of the product a yellow solid was obtained which when crystallized from benzene–ligroin melted at 130–155°. For purification this was converted into the trinitrobenzene derivative. After three crystallizations from benzene, which raised the melting point to 227–228°, this was decomposed by adsorption of the nitro component on alumina from benzene. After one crystallization from ligroin and two from ether–absolute alcohol, the hydrocarbon formed yellow plates, m. p. 215.7–216.2°; yield, 75 mg. (2%).

Anal. Calcd. for $C_{21}H_{14}$: C, 94.70; H, 5.30. Found: C, 94.89; H, 5.16.

The **picrate** formed purplish-black needles from benzene–ligroin, m. p. 207–208° (Found: N, 8.51), and the **trinitrobenzene derivative** formed short, brick-red needles from the same solvent mixture, m. p. 230–231° (Found: N, 8.58).

3,4-Benzpyrene-5-aldehyde.—A mixture of 1 g. of 3,4-benzpyrene, 1.1 g. of methylformanilide, 1.1 g. of phosphorus oxychloride, and 1 cc. of *o*-dichlorobenzene was warmed on the steam-bath for two hours; the solution became deep red and hydrogen chloride was evolved. The reaction mixture was poured into an aqueous solution of 5 g. of sodium acetate crystals and the solvent was removed with steam. The residual crystalline solid on crystallization from glacial acetic acid gave 1 g. (90%) of orange-yellow plates, m. p. 201–203°, and after two more crystallizations from benzene–ligroin the melting point was raised to 202.5–203.5°.

Anal. Calcd. for $C_{21}H_{12}O$: C, 90.00; H, 4.32. Found: C, 89.58; H, 4.39.

The **hydrazone** was prepared by adding 1 cc. of hydrazine hydrate in alcohol to a hot solution of 0.45 g. of the aldehyde in the minimum amount of dioxane. After warming for five minutes, more alcohol was added until the product began to crystallize. The hydrazone separated as fine yellow needles, m. p. 219.5–220.5°, dec. Since further crystallization from dioxane–alcohol resulted in decomposition, the original crystallizate, after thorough washing with alcohol, was analyzed.

Anal. Calcd. for $C_{21}H_{14}N_2$: N, 9.52. Found: N, 9.57.

For conversion to **5-methyl-3,4-benzpyrene**, 0.35 g. of the hydrazone was heated with a solution from 1 g. of sodium and 5 cc. of absolute alcohol for ten hours at 210–215°. The product was obtained directly as a solid; it was purified by passage of a benzene solution through a tower of alumina and crystallized from ether–absolute alcohol, giving 0.22 g. (70%) of yellow plates melting at 216.2–216.7° and giving no depression when mixed with the sample obtained from the methyllithium reaction product.

Summary

Methylcholanthrene and 3,4-benzpyrene are oxidized very readily by lead tetraacetate and seem to be more susceptible to attack by this reagent than other polynuclear hydrocarbons studied. 3,4-Benzpyrene gives a single monoacetoxy derivative in nearly quantitative yield, and methylcholanthrene is converted chiefly into the 15-acetoxy compound and in smaller part into 15-keto-20-methylcholanthrene.

On reaction with methylformanilide, 3,4-benzpyrene is converted in excellent yield into a single product which probably is the 5-aldehyde. This has been related to one of two new methyl-3,4-benzpyrenes obtained from products of the addition of methyllithium to a synthetic trimethylbenzanthrone and regarded as the 5- and 6-isomers.

The behavior of polynuclear hydrocarbons in the lead tetraacetate oxidation, aldehyde reaction, and diazo coupling test shows that the most powerfully carcinogenic hydrocarbons of the series possess special susceptibility to substitutions, and certain indications are discernible of a relationship between this specific type of chemical reactivity and carcinogenic activity.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASS. RECEIVED AUGUST 4, 1938

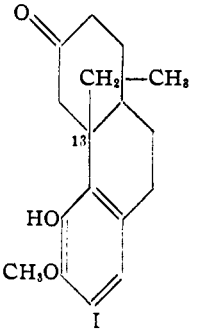
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Phenanthrene and Hydrophenanthrene Derivatives. VIII. Substances Related to Degradation Products of Morphine

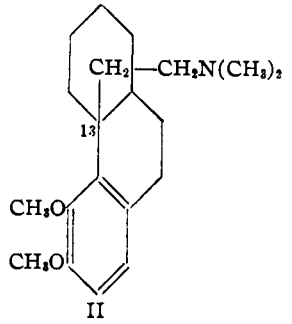
BY LOUIS F. FIESER AND H. L. HOLMES

In a previous paper[1] we described a diene synthesis by which it is possible to obtain hydrophenanthrene derivatives having a carboxyl group at a quaternary carbon atom corresponding to the 13-position of the morphine alkaloids. According to the Gulland–Robinson formula for morphine, these alkaloids contain an ethanamine chain joined at the hydrocarbon end to the 13-position of the hydrophenanthrene skeleton, but the exact position of attachment is the one remaining point of uncertainty concerning the structures. The new synthesis provides a possible method of obtaining compounds of known structure which, if the Gulland–Robinson formula is correct, may be obtainable from the alkaloids by degradation, and in the present work we have investigated the possibility of synthesizing suitable compounds.

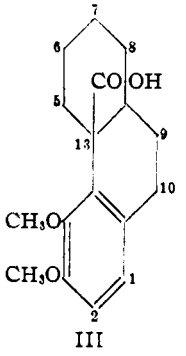
Degradative work on the alkaloids has not as yet provided many substances which seem within reach by the diene synthesis. A ketoethyloctahydromorphenol methyl ether of the probable structure I (Gulland–Robinson formulation) was obtained by Wieland and Kotake[2] and by Cahn[3] by various degradations, but Cahn encountered difficulties on attempting to reduce the carbonyl group and to methylate the compound. Speyer and Koulen[4] obtained as the methiodide a substance described as dihydrodesoxytetrahydro-α-methylmorphimethine and probably having the structure II, but an attempted Hofmann degradation to the corresponding vinyl compound apparently proceeded anomalously with demethylation at the 4-position and ring formation between the liberated hydroxyl and vinyl groups.[5] Our first



I



II



III

objective was the synthesis of the acid III, which may be obtainable from these or other degradation products, and we also made some study of possible methods of lengthening the carbon side chain.

The synthesis of 3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylic acid (III) was accomplished by application of the scheme of synthesis previously described. γ-(3,4-Dimethoxyphenyl)-butyric acid (IV) was prepared from veratrole by condensation with succinic anhydride and reduction, by the procedures already reported.[6,7] This acid undergoes cyclization very readily at the position para to one of the methoxyl groups,[8,9] and since it was

(1) Fieser and Holmes, THIS JOURNAL, **58**, 2319 (1936).
(2) Wieland and Kotake, *Ann.*, **444**, 69 (1925).
(3) Cahn, *J. Chem. Soc.*, 702 (1930).
(4) Speyer and Koulen, *Ann.*, **438**, 34 (1924).
(5) Cahn, *J. Chem. Soc.*, 2562 (1926).
(6) Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).
(7) Martin, *ibid.*, **58**, 1438 (1936).
(8) Haworth, *J. Chem. Soc.*, 1485 (1932).
(9) Haworth, Mavin and Sheldrick, *ibid.*, 1423 (1934).