

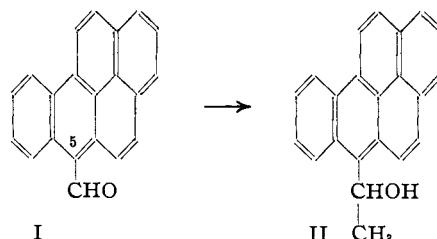
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Orientation of 3,4-Benzpyrene in Substitution Reactions

By LOUIS F. FIESER AND E. B. HERSHBERG¹

The chief objective of this work was to establish the orientation of 3,4-benzpyrene in the remarkable substitution reactions encountered in the diazo coupling² of the hydrocarbon and in its facile oxidation with lead tetraacetate to a mono-acetoxy derivative.³ The nitration reaction described by Windaus and Rennhak⁴ also came under consideration, for our *p*-nitrobenzeneazo compound on reduction gave an amine identical with that prepared⁴ from the nitro compound. It was shown previously³ that the reaction with methylformanilide gives the 5-aldehyde (I) by correlation of this with the synthetic 5-methyl compound,⁵ and Windaus and Raichle⁶ have recently related a new chloro derivative to the 5-aldehyde by conversion of both substances to the same nitrile. Various obvious methods of correlating the amine, phenol, and nitrile were tried without avail in the present work. The diazotization proceeds abnormally, and neither the Bucherer reaction nor its reversal could be accomplished, apparently because of the high sensitivity of the hydroxy compound.

For comparison of the 5-aldehyde with the acetylbenzpyrene of Windaus and Rennhak,⁴ the former compound was condensed with a Grignard reagent to the methyl carbinol II and the latter



was reduced catalytically. (The aldehyde proved resistant to oxidation and the nitrile to reaction with methylmagnesium chloride or bromide.) The two carbinols are isomers, which shows that the acetyl group is not located at C₅. This substantiates the more extensive evidence subsequently presented by Windaus and Raichle,⁶

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

(2) Fieser and Campbell, *THIS JOURNAL*, **60**, 1142 (1938).

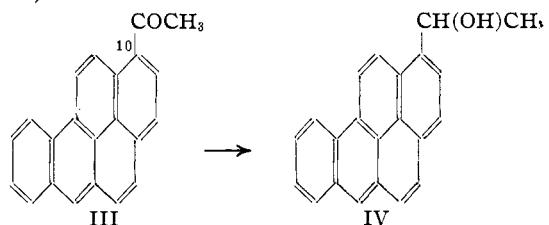
(3) Fieser and Hershberg, *ibid.*, **60**, 2542 (1938).

(4) Windaus and Rennhak, *Z. physiol. Chem.*, **249**, 256 (1937).

(5) Fieser and Hershberg, *THIS JOURNAL*, **60**, 1658 (1938).

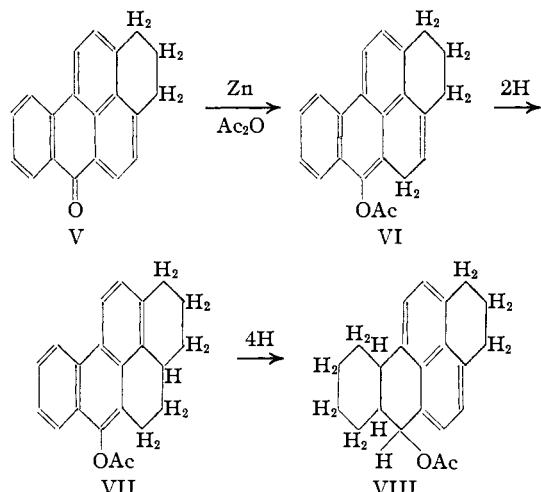
(6) Windaus and Raichle, *Ann.*, **537**, 157 (1938).

which leaves open only the 9- and 10-positions for the acetyl group, with preference for the latter (III).



The second carbinol therefore is probably IV.

It seemed likely that the hydroxybenzpyrene obtained from the lead tetraacetate reaction is the 5-isomer and that this might be proved by correlation with the synthetic benzanthrone derivative⁵ V, in which the oxygen atom is known to be in a corresponding position. Attempted dehydrogenation of V itself with sulfur resulted only in tars,



and it then seemed desirable to first convert the ketone into a derivative having a protected hydroxyl group. A method of obtaining such a substance was suggested by Scholl's observations⁷ characterizing the relationship of benzanthrone to its dihydride as similar to that in a quinone-hydroquinone system. Applying the method of reductive acetylation familiar in quinone chemistry, we found that the benzanthrone V can be converted with zinc dust, acetic anhydride, and sodium acetate into 5-acetoxytetrahydro-3,4-

(7) Scholl and Lenz, *Ber.*, **44**, 1666 (1911); Scholl, *ibid.*, **71**, 400 (1938).

benzpyrene (VI). Dehydrogenation of this substance under sparing conditions was conducted with a palladium oxide catalyst in acetic acid at 300°, but the sole product was benzpyrene. The enol acetate VI is too sensitive a substance to be methylated, but saturation of the non-benzenoid double bond by hydrogenation gave a more stable hexahydride which is assigned the phenanthrenoid structure VII. This could be hydrolyzed to a stable phenol, and treatment with a Grignard reagent followed by dimethyl sulfate gave the methyl ether. The 5-methoxyhexahydrobenzpyrene, however, likewise gave only benzpyrene on dehydrogenation by the above method, indicating the great lability of the 5-substituent.

The next scheme tried was to see if the synthetic ketone V and the hydroxybenzpyrene of unknown structure could be converted into identical hydrogenation products, the former compound already having been converted into the tetra- and hexahydro compounds VI and VII. On exhaustive hydrogenation of VII in acetic acid solution in the presence of platinum-palladium catalyst and a trace of ferrous chloride there was obtained an acetoxydecahydrobenzpyrene which is tentatively assigned the formula VIII. Whereas the hexahydride VII on saponification yielded a phenolic substance, the more highly hydrogenated derivative gave an alcohol. Measurements of the ultraviolet absorption spectrum in absolute alcohol of the hydroxy compound and of the other

substances mentioned below were kindly made by Miss Rachel G. Franklin of the Biochemical Research Laboratories of the Franklin Institute. The curve for the compound shown in Fig. 1 resembles that of naphthalene⁸ except that the characteristic absorption bands are shifted 25-30 m μ toward the red end of the spectrum. The spectrum seems consistent with the structure VIII, for this contains a tetraalkylated naphthalene nucleus, and it therefore appears that the further hydrogenation of the hexahydride VII is accompanied by a migration of certain of the original hydrogens to give a perhaps more stable structure.

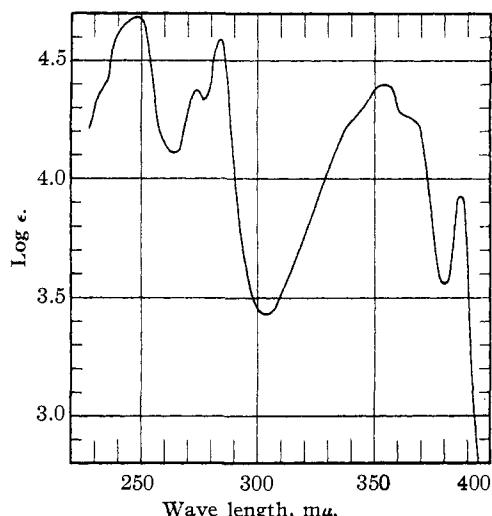


Fig. 2.—5-Hydroxy-1',2',3',4'-tetrahydro-3,4-benzpyrene (see X).

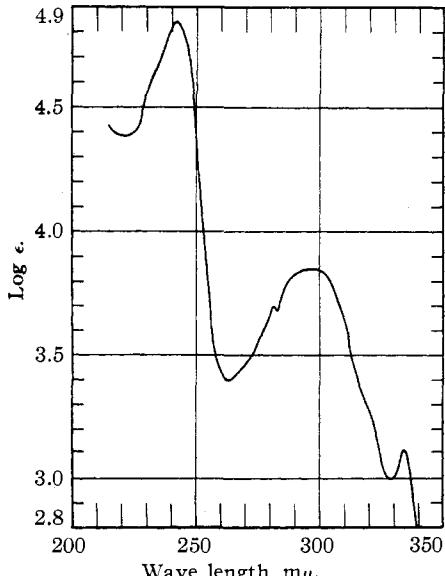


Fig. 1.—5-Hydroxydecahydro-3,4-benzpyrene (see VIII).

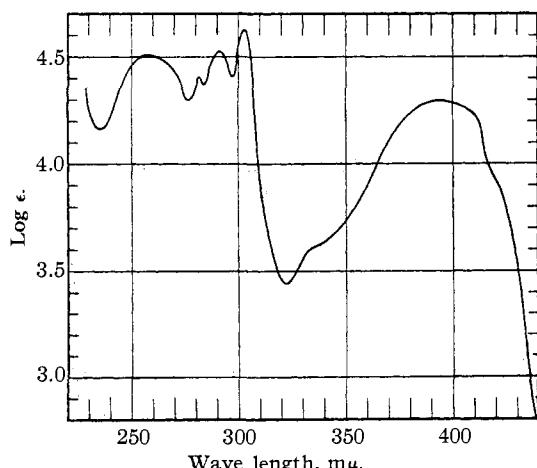
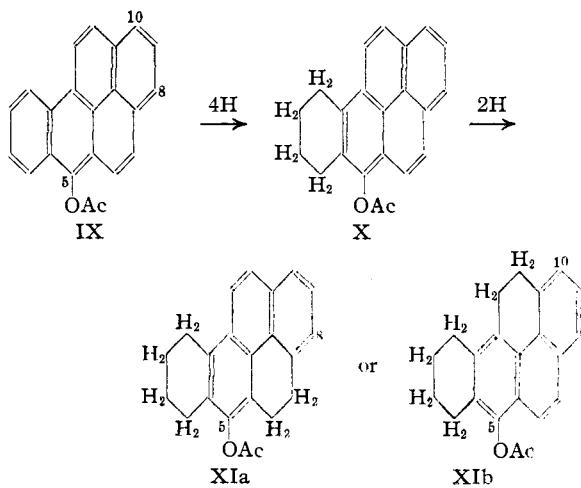


Fig. 3.—5-Hydroxybenzpyrene (see IX).

On hydrogenating acetoxybenzpyrene (IX) under similar conditions the initial product iso-

(8) Mayneord and Roe, *Proc. Roy. Soc. (London)*, A152, 299 (1935).

lated was a tetrahydride and, as expected in any case, this differed from the tetrahydride VI in the above series. The corresponding hydroxy compound is phenolic and its absorption spectrum (Fig. 2) differs appreciably from that of the parent, unhydrogenated substance (Fig. 3). The curve for the hydroxybenzpyrene resembles that of the hydrocarbon⁸ but shows less detail, particularly in the broad band in the region of longer wave length. The hydroxyl group of the tetrahydride also seems to blot out some of the fine detail in the spectra observable with polynuclear aromatic hydrocarbons, but if allowance is made for this factor a fair correspondence is discernible with the spectrum of pyrene,⁸ which suggests that it is the terminal, unsubstituted ring of the anthracenoid system which has been saturated with hydrogen (X). The hydrogenation thus follows the same course as established for 1,2-benzanthracene.⁹ On pushing the hydrogenation to an apparent end-point for the conditions used, one more mole of hydrogen was absorbed and the



product was a hexahydride which gave a phenol on saponification. The spectrum of this substance (Fig. 4) is suggestive of the presence of a phenanthrol unit as the absorbing center, as can be seen from a comparison of the curve with that for the above hexahydride VII (Fig. 5). The alternative formulas **XIa** and **XIb** give equally plausible locations for the added hydrogen atoms which fulfill the requirements of the spectrum, and a distinction cannot be made between them.

That neither the tetra- nor hexahydride in this series corresponded with the isomers obtained from the reference ketone V of known structure

(9) Fieser and Hershberg, THIS JOURNAL, 59, 2502 (1937).

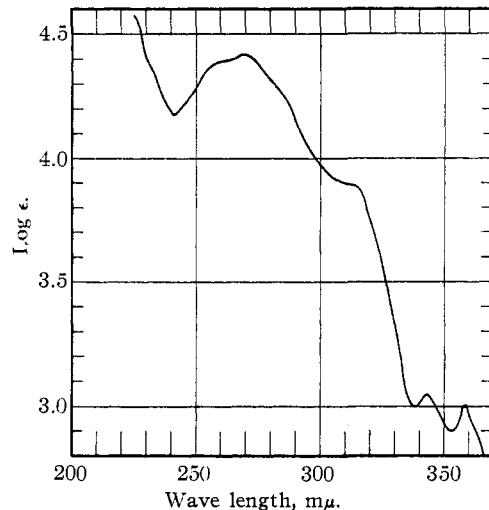


Fig. 4.—5-Hydroxy-1',2',3',4',(6,7 or 1,2)-hexahydro-3,4-benzpyrene (see **XIa** or **b**).

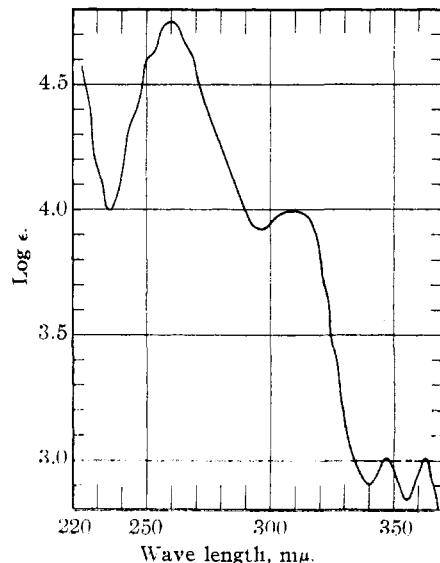


Fig. 5.—5-Hydroxy-6,7,7a,8,9,10-hexahydro-3,4-benzpyrene (see **VII**).

does not constitute evidence that the position of the oxygen substituent is different in the two series in view of the indications that the hydrogen atoms are differently situated; the failure to obtain identical products merely eliminated this line of attack on the problem of orientation. Of no more avail was a comparison of the properties of the phenolic substances corresponding to the acetates **IX**, **X**, and **XI**, and the hexahydride **VII** of the other series. Coupling tests with *p*-nitrobenzenediazonium chloride were either negative or resulted in the formation of diazo ethers, as recognized by cleavage to the components with

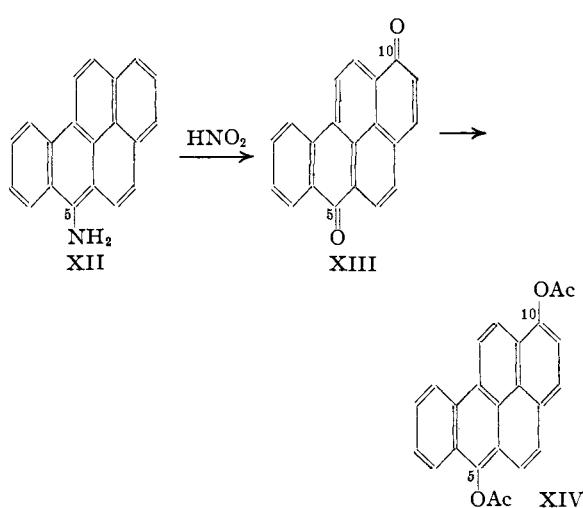
mineral acids, and there was no indication of the formation of hydroxyazo compounds either in alkali or in acetic acid solution. This observation, however, does not cast much light on the problem. Since it is known that 3-hydroxypyrene fails to couple to give an azo compound,¹⁰ a hydroxybenzpyrene with the substituent in either the 5, 8 or 10-position might be expected to behave similarly. The situation is the same with regard to the hydroxytetrahydrobenzpyrene corresponding to X. If, in the hexahydride, the disposition of the hydrogen atoms is that shown in formula XIa, no coupling would be expected for a 5-hydroxy compound, because no ortho or para positions are available, or for an 8-hydroxy derivative, because the only normal ortho position in the 3-phenanthroloid system would be blocked by an alkyl substituent.¹¹ For the alternate arrangement of hydrogen atoms (XIb), the choice would be open between positions 5 and 10 as the location for the hydroxyl group. The above observations merely show that benzpyrene is substituted by lead tetraacetate in one of the positions (5, 8, or 10) which Vollmann and co-workers¹⁰ established as the sites susceptible to attack on more drastic oxidation.

In seeking to relate our hydroxybenzpyrene with Windaus and Rennhak's amine, obtained through both the nitro and the *p*-nitrobenzeneazo derivatives, we attempted to diazotize this amine (XII) under various conditions. A diazonium salt could not be obtained, however, and the surprising observation was made that the amine is converted by the action of nitrous acid in acetic-

sulfuric acid solution into 3,4-benzpyrene-5,10-quinone¹⁰ (XIII), identified in the form of the more sharply characterized hydroquinone diacetate¹⁰ (XIV). While Vollmann and co-workers¹⁰ found that oxidation of the hydrocarbon itself gives a mixture of the 5,10- and 5,8-quinones, which were separated through the reductive diacetates, the material from the amine seemed to consist entirely of the 5,10-isomer. A diazotization of the amine does not seem to be involved as an essential step in the unusual reaction, for under the same conditions hydroxybenzpyrene is likewise converted by nitrous acid into the 5,10-quinone. Possibly both reactions proceed through the formation of the 10-nitroso derivative,¹² followed by hydrolysis. The observations limit the possible locations for both the amino and hydroxyl groups to the 5- and 10-positions.

A significant inference can be made from the evidence of the above results combined with an observation reported in the recent paper of Windaus and Raichle.⁶ These workers converted their acetylbenzpyrene (III) by Beckmann rearrangement of the oxime and hydrolysis into an aminobenzpyrene different from that which Windaus and Rennhak had obtained from the nitro compound. On their evidence the new isomer very probably is the 10-isomer, and although their results did not completely exclude the 9-position an additional observation of the present work which will be mentioned below supplies the completing evidence and shows that the Windaus and Raichle compound definitely is 10-amino-3,4-benzpyrene. Since the Windaus and Rennhak amine differs from this substance and has now been shown to be either a 5- or 10-derivative, it can be assigned the structure of 5-amino-3,4-benzpyrene (XII).

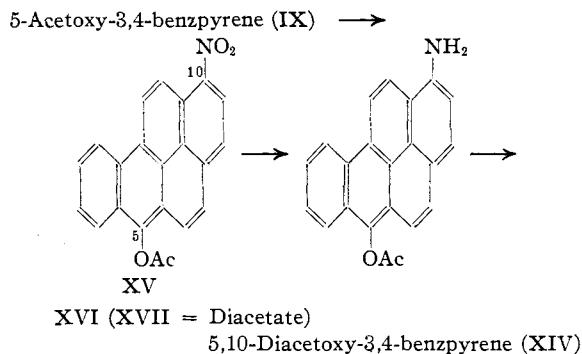
When acetoxybenzpyrene (IX) was treated as before with isoamyl nitrite in acetic-sulfuric acid solution there resulted in good yield an orange-product which proved to be a nitro acetoxybenzpyrene (XV), and it was then found that the same substance can be obtained by gentle nitration with nitric acid in acetic acid solution. The nitro compound gave an amine (XVI) on catalytic hydrogenation, and this was hydrolyzed by prolonged refluxing with dilute sulfuric acid to give, after acetylation (reductive), a product identical with 5,10-diacetoxy-3,4-benzpyrene (XIV). The substituents therefore are located as above in the 5- and 10-positions.



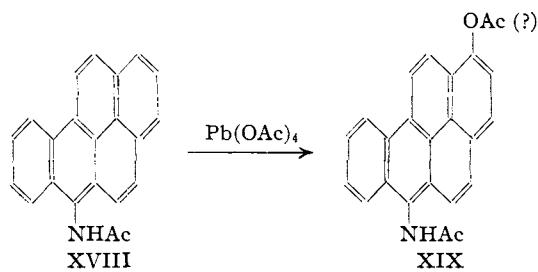
(10) Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

(11) Fieser and Young, *THIS JOURNAL*, **53**, 4120 (1931).

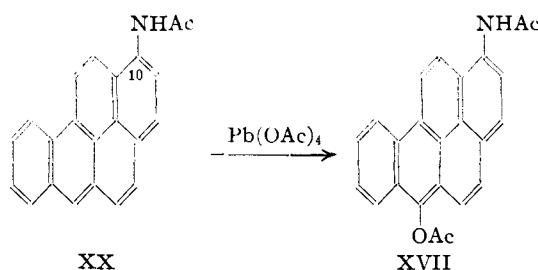
(12) Blangey, *Helv. Chim. Acta*, **21**, 1579 (1938).



It next seemed possible that a 5,10-disubstituted hydroxyamine diacetate isomeric with the substance XVII might be obtained starting with the 5-amine as a reference substance. The amine was therefore oxidized in the form of the acetate (XVIII) with lead tetraacetate and a compound of the expected composition isolated. This differs from the isomer XVII and probably has the structure XIX, but all attempts to establish



the position of the new substituent by conversion to a known quinone or diacetoxy compound were unsuccessful. We finally undertook to prepare a hydroxyamine diacetate expected to be identical



with the above 5,10-derivative XVII starting with Windaus and Raichle's 10-amino-3,4-benzpyrene. The acetylamine XX reacted smoothly with lead tetraacetate and indeed gave XVII. The 5,10-relationship of the substituents having been established as stated above by conversion to the known diacetoxybenzpyrene, the new observation proves that the Windaus and Raichle compound is the 10-amine and not the 9-isomer. Furthermore, it is now clear that the substituent

introduced in the nitration of the acetoxybenzpyrene enters the same position 10 and, consequently, that the acetoxy group must be located at the alternate position 5.

It can be concluded that 3,4-benzpyrene is substituted exclusively in the 5-position on oxidation with lead tetraacetate, in the diazo coupling reaction, on nitration, chlorination, and condensation with methylformanilide. The only reaction known to follow a different course is the Friedel and Crafts condensation with acetyl chloride studied by Windaus and his co-workers, and the acetyl derivative which they isolated is characterized fully on the present evidence as the 10-isomer. While Windaus and Raichle report the isolation of this isomer in 66% yield using a deteriorated sample of aluminum chloride as catalyst, the samples which we prepared by a slightly different procedure (stannic chloride) invariably consisted of mixtures of isomers from which pure 10-acetylbenzpyrene was isolated only by a rather lengthy process of purification. In one experiment the mother liquor material was further fractionated both as such and as the oxime. A homogeneous oxime was collected in one fraction and on Beckmann rearrangement it gave a well-defined acetylaminobenzpyrene different from the known 5- and 10-isomers. This may well be the 8-isomer. At any rate it is evident that in the Friedel and Crafts reaction substitution occurs largely but not exclusively in the 10-position, and that if the more reactive but also more hindered 5-position is attacked at all this must occur to a very minor extent.

It is of interest that the 5-position is the center predicted from the bond structure favored¹³ for the hydrocarbon to be the most reactive, for it is at one end of the quinonoid system of double bonds and, in contrast to the 8-position, it is subject to the activating influence of the adjacent 3,4-benz nucleus. This however cannot be cited as an argument in support of the suggested arrangement of bonds, for the same position would be expected to show special reactivity on the basis of the alternate benzanthenoid bond structure.

Experimental Part¹⁴

5-Hydroxy-3,4-benzpyrene.—A Grignard solution was prepared from 3.9 g. of *n*-butyl bromide and 0.8 g. of magnesium in ether and 1.4 g. of crystalline 5-acetoxyben-

(13) Fieser and Seligman, THIS JOURNAL, 60, 170 (1938).

(14) All melting points are corrected except those above 300°, which were determined with a metal block. Microanalyses by Lyon Southworth and the Arlington Laboratories (*).

pyrene³ was added to the stirred solution. The solid dissolved readily, and after refluxing overnight dilute hydrochloric acid was added. The ether layer was clarified with Norite, concentrated, and diluted with ligroin. The crystallizate of the hydroxy compound amounted to 0.98 g. (81%) and the material melted at 207–209° dec., when the sample was introduced to a bath at 205° and heated rapidly. On repeated recrystallization from ether-ligroin the substance formed clusters of fine tan needles of the same m. p.

*Anal.** Calcd. for C₂₀H₁₂O: C, 89.38; H, 4.51. Found: C, 89.75; H, 4.85.

The hydroxy compound is readily soluble in alcohol or benzene. It dissolves in aqueous alkali on warming to give initially a clear yellow solution; alteration soon occurs, however, for the solution rapidly becomes cloudy and deposits a flocculent brown precipitate. 5-Hydroxybenzpyrene dissolves in concentrated sulfuric acid to an intensely crimson solution. The substance shows no sign of coupling with *p*-nitrobenzenediazonium chloride in alkaline solution and in acetic acid solution the addition of the nitrous acid-free reagent produces merely a brown coloration.

5-Methoxy-3,4-benzpyrene.—A 1-g. sample of the acetoxy compound was refluxed for three hours with the Grignard reagent from 2.2 g. of *n*-butyl bromide, 18 g. of dimethyl sulfate was added in benzene solution, the ether was displaced by benzene and refluxing was continued for twenty hours. The mixture was then stirred for four hours with excess 6 N sodium hydroxide and acidified, and the benzene layer was dried and passed through a tower of alumina. The material obtained from the concentrated filtrate was crystallized from ether-ligroin, giving 0.53 g. (58%) of material, m. p. 165–170°. Three further crystallizations from benzene-ligroin gave clusters of small, light yellow plates melting constantly at 174–174.5°.

*Anal.** Calcd. for C₂₁H₁₄O: C, 89.33; H, 5.00. Found: C, 89.24; H, 5.02.

5-Acetoxy-1',2',3',4'-tetrahydro-3,4-benzpyrene (X).—A solution of 1.55 g. of 5-acetox-3,4-benzpyrene in 100 cc. of ethyl acetate and 50 cc. of glacial acetic acid with 75 mg. of Adams catalyst (in two portions) containing added palladium absorbed two moles of hydrogen in forty-two hours. The collected product on one crystallization from benzene-ligroin gave 1.05 g. (67%) of plates, m. p. 176.5–178.5°. On two more crystallizations the substance formed colorless plates, m. p. 182–183°.

*Anal.** Calcd. for C₂₂H₁₈O₂: C, 84.03; H, 5.78. Found: C, 83.92; H, 5.74.

Dehydrogenation of the tetrahydride (50 mg.) with palladium oxide catalyst (5 mg.) in acetic acid (5 cc.) at 300° gave only benzpyrene (26 mg.).

5-Hydroxy-1',2',3',4'-tetrahydro-3,4-benzpyrene.—The acetate X (0.47 g.) was refluxed for one-half hour with 2% methyl alcoholic potassium hydroxide and the phenolic reaction product precipitated by diluting with water and acidifying. The substance is sensitive to oxidation and was first crystallized from dilute methanol containing a little stannous chloride, giving 250 mg., m. p. 181–182°, and 75 mg., m. p. 176–178°. The best material from

dilute methanol formed weakly greenish yellow, diamond-shaped prisms, m. p. 181.5–182°.

Anal. Calcd. for C₂₀H₁₆O: C, 88.21; H, 5.92. Found: C, 88.19; H, 5.90.

The addition of *p*-nitrobenzenediazonium chloride to a solution of the phenol in aqueous alkali caused the separation of a light yellow precipitate. This was decomposed on warming with hydrochloric acid and thus appears to be a diazo ether. In coupling tests in acetic acid solution a green coloration was produced, changing to brown, and there was no indication of the formation of an azo dye.

5-Acetoxy-1',2',3',4'-(6,7 or 1,2)-hexahydro-3,4-benzpyrene (XI a or b).—A suspension of 1 g. of 5-acetox-3,4-benzpyrene in 100 cc. of glacial acetic acid in the presence of 200 mg. of platinum-palladium catalyst (in three portions) absorbed 380 cc. of hydrogen in forty-six hours. The product was initially gummy, but crystallization from benzene-ligroin gave 0.34 g., m. p. 130–132.5°, and 0.09 g., m. p. 127–129° (yield, 42%). On three further crystallizations from ligroin it formed colorless cubes having a blue fluorescence, m. p. 135.5–136°.

*Anal.** Calcd. for C₂₂H₂₀O₂: C, 83.48; H, 6.39. Found: C, 83.54; H, 6.46.

5-Hydroxy-1',2',3',4'-(6,7 or 1,2)-hexahydro-3,4-benzpyrene.—Saponification of XI as usual gave a phenolic substance which when crystallized from dilute methanol containing stannous chloride formed faintly pinkish prisms, m. p. 139.5–140°. The compound is soluble in alkali and behaves in the coupling test like the tetrahydride.

*Anal.** Calcd. for C₂₀H₁₈O: C, 87.57; H, 6.62. Found: C, 87.15; H, 6.88.

5-Acetoxy-6,8,9,10-tetrahydro-3,4-benzpyrene (VI).—2,1'-Trimethylene-1,9-benzanthrone-10⁵ (0.5 g.) was mixed with fused sodium acetate (0.5 g.) and heated to boiling with 15 cc. of acetic anhydride and zinc dust (2 g.) was added in portions over a fifteen-minute period. Acetic acid in equal volume was then added and the pale yellow solution was decanted from the zinc dust, which was then extracted with more solvent. Water was added cautiously to the combined solution to decompose the excess anhydride and then to the point of saturation. The product separated as light yellow needles amounting to 0.51 g. (88%), m. p. 166.5–167.5°. The melting point rose to 168.5–169° on recrystallization from dilute acetic acid and remained unchanged on further purification from acetic acid or from benzene-ligroin.

Anal. Calcd. for C₂₂H₁₈O₂: C, 84.03; H, 5.80. Found: C, 84.11; H, 5.88.

A 0.75-g. sample of the acetate was heated for two hours with shaking at 300° in a sealed tube with 75 mg. of palladium oxide catalyst and 15 cc. of glacial acetic acid. There was obtained 0.42 g. (70%) of benzpyrene.

5 - Acetoxy - 6,7,7a,8,9,10 - hexahydro - 3,4 - benzpyrene (VII).—A fine suspension was produced by dissolving 1.45 g. of the above acetate VI in a warm mixture of 50 cc. each of ethyl acetate and glacial acetic acid and cooling rapidly; 25 mg. of platinum-palladium catalyst was added and on shaking with hydrogen the character of the suspended material slowly changed. One mole of

gas was absorbed after seven hours, although solution was not complete. The solid was dissolved by warming and the solution was clarified with Norite, filtered, concentrated and diluted with water. There was obtained 1.02 g. (70%) of solid, m. p. 178–179°. Four crystallizations from benzene-ligroin gave flat, colorless plates, m. p. 182.8–183.3°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.48; H, 6.39. Found: C, 83.65; H, 6.35.

5 - Hydroxy - 6,7,7a,8,9,10 - hexahydro - 3,4-benzpyrene was obtained by refluxing the acetate VII (0.48 g.) with 50 cc. of methanol and 0.5 g. of potassium hydroxide for one hour, diluting with water, and precipitating the product from the clear brownish solution by acidification. Crystallization from dilute alcohol gave small, pale yellow plates, m. p. 163–164°. In coupling tests the substance appeared to give a diazo ether which could be cleaved with acid.

*Anal.** Calcd. for $C_{20}H_{18}O$: C, 87.57; H, 6.62. Found: C, 87.35, 87.27; H, 6.80, 6.77.

5 - Methoxy - 6,7,7a,8,9,10 - hexahydro - 3,4 - benzpyrene.—The acetate VII (0.9 g.) was cleaved with *n*- C_4H_9MgBr and methylated as described for the preparation of methoxybenzpyrene and the material recovered after filtration through an alumina tower was crystallized from ether-methanol, giving 0.44 g. (54%) of ether, m. p. 133–135°. Recrystallization gave colorless microcrystals, m. p. 135.5–136.5°.

*Anal.** Calcd. for $C_{21}H_{20}O$: C, 87.45; H, 7.01. Found: C, 87.64; H, 7.38.

Attempted dehydrogenation with sulfur in boiling quinoline gave no definite product. On heating the substance with palladium charcoal for two hours at 270–275° there was obtained chiefly unchanged ether together with a little benzpyrene.

5-Acetoxydecahydro-3,4-benzpyrene (VIII?).—A solution of 0.79 g. of the acetoxyhexahydride VII in 50 cc. of glacial acetic acid was shaken with hydrogen in the presence of 125 mg. of platinum-palladium catalyst, added in two portions, and a drop of 1% ferrous chloride solution. The reaction stopped after the absorption of 138 cc. of hydrogen in twenty hours, even after the addition of fresh catalyst. The clear, colorless solution after being filtered, concentrated, and diluted afforded 0.6 g. (76%) of product, m. p. 120–122°. Two crystallizations from ligroin gave long, glistening, colorless needles, m. p. 124–126°.

*Anal.** Calcd. for $C_{22}H_{24}O_2$: C, 82.46; H, 7.56. Found: C, 82.28; H, 7.60.

5-Hydroxydecahydro-3,4-benzpyrene.—After refluxing the acetate VIII (0.3 g.) with methanol (25 cc.) and potassium hydroxide (0.5 g.) for one hour the hydrolysis product separated in a crystalline condition, m. p. 167–168°, on dilution with water (0.23 g., 89%). The melting point was unchanged on further crystallization from benzene-ligroin and from dilute methanol. The substance forms pale yellow, fine, matted needles. It does not dissolve in aqueous alkali, and the addition of alkali does not appear to increase the solubility in alcohol.

*Anal.** Calcd. for $C_{20}H_{20}O$: C, 86.28; H, 7.98. Found: C, 86.31; H, 7.87.

3,4-Benzpyrene-5-aldehyde-oxime.¹⁵—An excess of hydroxylamine in methanol was added to a solution of 0.5 g. of the aldehyde⁶ in dioxane and after refluxing for ten minutes water was added to the point of saturation. The oxime crystallized as glistening, light yellow leaflets, m. p. 242–244°, dec.; yield, 0.42 g. (83%). Recrystallized from dilute dioxane it melted at 241–243°, dec.

Anal. Calcd. for $C_9H_{12}ON$: N, 4.76. Found: N, 4.98.

3,4-Benzpyrene-5-nitrile¹⁵ was obtained by refluxing 0.31 g. of oxime with 10 cc. of acetic anhydride for fifteen minutes and adding acetic acid to the point of saturation; the product (0.27 g., 92%), m. p. 237–238°, when recrystallized from acetic acid formed small yellow needles, m. p. 237.4–237.7°.

Anal. Calcd. for $C_{11}H_{11}N$: N, 5.05. Found: N, 5.12.

Methyl-3,4-benzpyrenyl-5-carbinol (II) was prepared by adding 3.3 g. of benzpyrene-5-aldehyde in 75 cc. of benzene to an ethereal solution of methylmagnesium chloride from 0.6 g. of metal; the ether was largely evaporated and refluxing was then continued for three hours before hydrolysis with cold ammonium chloride solution. The benzene extract was passed through a tower of alumina, a brown layer at the top was discarded, as was a narrow orange layer at the bottom and a layer showing bluish white fluorescence in ultraviolet light. The carbinol was adsorbed in a broad yellow zone at the center and this was separated and eluted with hot benzene-methanol. The oil remaining on evaporation of the filtrate was dissolved in ether and caused to crystallize by the addition of hexane. Two crops of carbinol were obtained in the form of yellow agglomerates, m. p. 142–143° (78% yield); two more crystallizations gave ball-like clusters of yellow microcrystals, m. p. 141–141.5°.

Anal. Calcd. for $C_{21}H_{18}O$: C, 89.17; H, 5.43. Found: C, 89.03; H, 5.57.

In an attempted oxidation with hypoiodite in warm dioxane solution the carbinol (0.9 g.) was recovered largely unchanged (0.6 g.).

5 - Nitro - 3,4 - benzpyrene.—Nitration according to Windaus and Rennhak⁴ in our hands gave satisfactory nitro compound in only 47% yield. The yield was raised to 81% by using only one-tenth of the nitric acid specified, and with only 1.25 mole of reagent the yield was likewise good and the product somewhat purer. It also seemed advantageous to add benzene to the mixture to keep the hydrocarbon in solution.

In a typical experiment a solution of 2 g. of benzpyrene in 50 cc. of benzene was diluted with 250 cc. of acetic acid and a solution of 0.63 cc. of nitric acid (sp. gr. 1.42) in 25 cc. of acetic acid was added rapidly and with good mixing. On standing undisturbed the solution first turned dark purple-red and the color then gradually lightened to orange. Crystallization of the yellow nitro compound began in about five minutes and was complete after one and one-half hours. After ice cooling the collected crude product weighed 1.9 g. (81%). A benzene solution of the material when passed through an alumina tower left only a small orange zone of dinitro compound (rejected) and the filtrate afforded 1.72 g. (73%) of pure, orange-yellow nitrobenzpyrene, m. p. 254–255°.

(15) Compare Windaus and Raichle, ref. 6.

In contrast to the material prepared by Windaus and Rennhak,⁴ our product was comparatively stable in solution and was unaffected by light over the working period.

5-Amino-3,4-benzpyrene. (a) **From the Nitro Compound.**—In view of the low yield reported by Windaus and Rennhak⁴ for the procedure of reduction with phenylhydrazine, another method was tried. A suspension of 1.58 g. of the nitro compound and 50 mg. of Adams catalyst in 75 cc. of ethyl acetate, after an initial and repeatedly observed induction period, absorbed the theoretical volume of hydrogen in thirty to forty minutes. After treatment with Norite and filtration the amine was obtained in two crops totalling 1.29 g. (91%) as glistening, golden yellow plates, m. p. 237–239°, dec. (235–236°, dec., in another experiment).

(b) **From 5-(*p*-Nitrobenzeneazo)-3,4-benzpyrene.**—A suspension of 85 mg. of the azo compound² in 20 cc. of alcohol was refluxed with 1 g. of crystalline stannous chloride and a few drops of hydrochloric acid for fifteen minutes, when the red color was discharged. Dilution with water gave a gelatinous precipitate which was washed by centrifugation and the moist solid was crystallized from dilute alcohol and then twice more from alcohol, giving golden yellow plates, m. p. 232–234°, dec. This did not depress the m. p. of the sample (a).

5-Acetylaminio-3,4-benzpyrene.—To avoid the formation of the diacetyl derivative, as in the experiment reported by Windaus and Rennhak,⁴ it was found advisable to use acetic acid as a diluent, but since the amine decomposes rapidly in this solvent at the boiling point ethyl acetate was used as a less destructive solvent to bring it into solution. Thus 0.31 g. of the amine was dissolved in 20 cc. of ethyl acetate and the solution was boiled down until solid began to separate (about 5 cc.), when 15 cc. of boiling acetic acid was added. As soon as the amine had redissolved, 0.1 g. of sodium acetate and 2 cc. of acetic anhydride were added. On slowly boiling the solution without reflux for about five minutes light yellow crystals of the acetylamine began to separate. Collected after cooling, the product amounted to 1.55 g. (89%) and was of satisfactory purity. Recrystallized from acetic acid it formed pale yellow leaflets, m. p. 345–350°, dec. (uncorr.).

Anal. Calcd. for $C_{22}H_{15}ON$: N, 4.53. Found: N, 4.47.

5-Acetylaminio-*x*-acetoxy-3,4-benzpyrene.—A solution of 0.155 g. of 5-acetylaminobenzpyrene in 50 cc. of acetic acid was treated at room temperature with 0.234 g. of lead tetraacetate in 10 cc. of acetic acid. Tests for the oxidizing agent with starch-iodide paper were faint after thirty minutes and negative in one hour. The solution was diluted with water until saturated at the boiling point. The yellow, amorphous material which separated was crystallized three times from dioxane-ligroin and obtained as a dull yellow, microcrystalline powder, m. p. 245–255°, dec. It gives a fluorescent orange-yellow coloration in sulfuric acid.

Anal. Calcd. for $C_{24}H_{17}O_3N$: C, 78.44; H, 4.67; N, 3.82. Found: C, 78.49; H, 4.30; N, 3.72.

Attempted hydrolysis by heating the diacetate with dilute sulfuric acid for one day under reflux or for ten hours at 170° gave no definite results.

5-Diacetylaminio-3,4-benzpyrene was obtained by refluxing the amine (0.15 g.) with acetic anhydride (20 cc.)

for two hours. The monoacetyl derivative first separated and then redissolved to give a pale yellow solution with a purplish fluorescence. The crude product (0.17 g., m. p. 219–221°) contained a little monoacetate which was left undissolved on crystallization from benzene-ligroin; the purified diacetate formed greenish yellow, diamond-shaped plates, m. p. 224.5–225.5° (Windaus and Rennhak⁴ give 217.5°, uncorr.). The substance seemed to be less readily attacked by lead tetraacetate than is the monoacetyl derivative and no reaction product was obtained.

Anal. Calcd. for $C_{24}H_{17}O_2N$: N, 3.99. Found: N, 3.96.

Conversion to 5,10-Diacetoxyl-3,4-benzpyrene. (a) **5-Amino-3,4-benzpyrene.**—A solution of 0.18 g. of the amine in 50 cc. of acetic acid and 2–3 cc. of 12 N sulfuric acid was treated with 0.5 cc. of amyl nitrite at 0–5°, when it immediately turned red and a brown solid separated. After fifteen minutes the mixture was poured into two volumes of dilute sulfuric acid. On warming the mixture a clear, deep red solution resulted and then, near the boiling point, a brown-red solid separated. The washed and dried material had the properties of the 5,10-quinone; for identification it was heated with zinc dust, sodium acetate, and acetic anhydride, affording 90 mg. of 5,10-diacetoxyl-3,4-benzpyrene,¹⁰ m. p. 241.5–242.5°. Three more crystallizations from benzene-ligroin raised the m. p. to 243.5–244.5° (fine, nearly colorless needles).

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.25; H, 4.38. Found: C, 78.25; H, 4.75.

(b) **5-Hydroxy-3,4-benzpyrene.**—Treated in exactly the same manner, the hydroxy compound (90 mg.) showed the same initial phase but on pouring the mixture into aqueous acid a clean orange precipitate separated and did not dissolve or undergo apparent change on boiling. Reductive acetylation of this material gave 53 mg. of 5,10-diacetoxyl-3,4-benzpyrene. After two crystallizations from benzene-ligroin the sample melted at 242–243° and there was no depression on admixture with the material from the amine.

5-Acetoxy-10-nitro-3,4-benzpyrene (XV).—In the most satisfactory procedure developed a solution of 0.16 cc. of nitric acid (sp. gr. 1.50) in 50 cc. of acetic acid was added to a solution of 1 g. of 5-acetoxylbenzpyrene in 200 cc. of acetic acid at a temperature of 40°. The solution turned orange and the orange nitro compound soon began to separate. After standing for two hours the solid was collected, washed with dilute acetic acid, and dried; yield 1.10 g. (96%), m. p. 257–259°, dec. After four crystallizations from acetic acid or benzene it formed fine orange needles, m. p. 259.5–260°, dec. An identical product was obtained in lower yield using isoamyl nitrite.

*Anal.** Calcd. for $C_{22}H_{18}O_4N_3$: C, 74.36; H, 3.69; N, 3.95. Found: C, 74.76, 74.67; H, 4.08, 3.98; N, 3.77.

5-Acetoxy-10-amino-3,4-benzpyrene (XVI).—A suspension of 2.15 g. of the nitro compound in 150 cc. of ethyl acetate with 25 mg. of Adams catalyst absorbed the theoretical amount of hydrogen in seven hours, the suspended material changing to a light yellow solid. This was dissolved by adding 50 cc. more solvent and warming, and the filtered solution when concentrated and treated with hexane afforded 1.71 g. (87%) of product, m. p.

221–222°. Recrystallization gave short, golden brown needles of the same m. p.

Anal. Calcd. for $C_{22}H_{15}O_2N$: N, 4.31. Found: N, 4.41.

For hydrolysis a suspension of 0.13 g. of finely powdered amine in 18 cc. of water containing 2 cc. of concentrated sulfuric acid was refluxed for sixteen hours. The solid changed in appearance and became dark reddish brown; it is possible that oxidation occurred during the heating and that the solid consisted largely of the quinone. The material was therefore dried and submitted to reductive acetylation. The crude reaction product was quite dark, but two crystallizations from benzene–ligroin with the use of Darco gave nearly colorless needles (8 mg.) of 5,10-diacetoxy-3,4-benzpyrene, m. p. 241–242°, identified by mixed m. p. with an authentic sample.

5 - Acetoxy - 10 - acetylaminoo - 3,4 - benzpyrene (XVII). (a) From 5-Acetoxybenzpyrene.—A solution of 0.2 g. of the amine XVI in 10 cc. of acetic anhydride was warmed almost to the boiling point, whereupon the yellow diacetate separated (0.15 g.), m. p. 320–325° (uncorr.). It was recrystallized by dissolving in dioxane and adding ligroin and obtained as a yellow solid of the same m. p. The material was seen to be crystalline when viewed under the microscope and gave a reddish-purple solution in sulfuric acid.

Anal. Calcd. for $C_{24}H_{17}O_3N$: N, 3.82. Found: N, 3.77.

(b) From 10-Acetylaminobenzpyrene.—In preparing the starting material 10-acetylbenzpyrene (0.575 g.) was converted into the oxime⁶ by refluxing for ten hours with methanol (75 cc.), hydroxylamine hydrochloride (0.3 g.) and sodium hydroxide (0.43 g.); the product separating on cooling weighed 0.595 g. (98%), m. p. 264–267°, dec. Rearranged exactly as described by Windaus and Raichle,⁶ 1.13 g. of oxime gave 0.65 g. (57%) of 10-acetylaminoo-3,4-benzpyrene, m. p. 334–337° dec. (uncorr.).

The oxidation proceeded much more readily than with the 5-isomer (above). A solution of 0.155 g. of the compound in 75 cc. of acetic acid was treated with 0.234 g. of lead tetraacetate in 10 cc. of acetic acid at room temperature, and after about two minutes the test with starch–iodide paper was negative. Water was added, giving a deep brown color, and after diluting the solution to the point of saturation at the boiling point an amorphous brown solid was obtained. This was crystallized twice by dissolving it in 100 cc. of dioxane, concentrating, and adding hexane. The product was obtained as a microcrystalline powder, m. p. 325–330°, dec. (uncorr.). It was reddish-purple in sulfuric acid. A mixture with the product described in (a) melted at 320–325°, dec. (uncorr.).

Acetylation of 3,4-Benzpyrene.—A cold solution of 3.6 g. of benzpyrene and 1.17 cc. of acetyl chloride in 50 cc. of nitrobenzene was treated with 4.9 cc. of stannic chloride in 25 cc. of nitrobenzene and the deep purplish red solution was held at 4° for sixty hours. After treatment with dilute hydrochloric acid the nitrobenzene layer was steam distilled and the dark solid dissolved in benzene. The ketone was then adsorbed on alumina and after removing a dark top layer from the column the remainder was eluted with benzene–methanol. The total crystallizate

amounted to 3.0 g. (72%) of a ketone mixture, m. p. 155–165°. Five crystallizations from acetic acid gave 1.1 g. (26%) of satisfactory 10-acetyl-3,4-benzpyrene,^{4,6} m. p. 186–188°. Further purification from benzene–hexane gave refractive, bright yellow needles, m. p. 190–190.5°.

Repeated crystallization of the material in the mother liquor from various solvents gave 1.3 g. of a ketone mixture, m. p. 149–154°, which resisted further attempts to effect a separation by fractionation. Consequently 0.88 g. of this mixture was converted into the oxime by refluxing overnight with 0.3 g. of hydroxylamine and 0.6 g. of sodium hydroxide in 100 cc. of methanol. The crude oxime was precipitated by the addition of dilute hydrochloric acid and crystallized from benzene. Some of the 10-acetoxime was present and was separated on partial crystallization as the least soluble fraction, and further amounts were removed by partial solution of the solid in hot benzene. After five crystallizations of the remaining material the principal, but apparently not the only, other substance present was obtained as aggregates of small yellow needles, m. p. 220–223° (0.15 g.). This has the composition of a *y*-acetyl-3,4-benzpyrene oxime.

Anal. Calcd. for $C_{22}H_{15}ON$: N, 4.53. Found: N, 4.47.

On Beckmann rearrangement, conducted as before, 0.13 g. of this oxime gave 60 mg. of *y*-acetylaminoo-3,4-benzpyrene, m. p. 269–270°, in the form of small, microcrystalline aggregates.

Anal. Calcd. for $C_{22}H_{15}ON$: N, 4.54. Found: N, 4.58.

Methyl-3,4-benzpyrenyl-10-carbinol (IV).—A suspension of 0.4 g. of the 10-acetyl compound in 20 cc. of ethyl acetate was hydrogenated in the presence of Raney nickel catalyst. The absorption of hydrogen proceeded very slowly, reaching 47 cc. after ten days. The product proved to be a mixture, but after several crystallizations from ether–hexane and from methanol a small amount of a homogeneous substance was isolated. This formed bright yellow prisms which melted initially over the range 146–153° but remelted sharply at 153–154° after solidification. A mixture with the 5-isomer (II) was depressed to 125–130°.

Anal. Calcd. for $C_{22}H_{16}O$: C, 89.17; H, 5.44. Found: C, 88.83; H, 5.50.

On attempted reduction of the ketone by refluxing for one day with aluminum isopropylate in benzene and slow distillation of the solvent, the starting material was recovered quantitatively.

Summary

It has been shown that the point of attack in the oxidation of 3,4-benzpyrene with lead tetraacetate, and in the diazo coupling and nitration of the hydrocarbon, is at the 5-position, as previously established for the condensation with methylformanilide and (by Windaus) for chlorination. Evidence supplementary to that adduced by Windaus fixes the structure of the chief product of acetylation as that of the 10-isomer.

The correlation of various monosubstituted benzpyrenes was rendered difficult by the unusual properties encountered in compounds of this series. Of special note is the conversion of the 5-

amino and 5-hydroxy derivatives into the 5,10-quinone on treatment with nitrous acid.

CONVERSE MEMORIAL LABORATORY

CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 23, 1939

[CONTRIBUTION NO. 154 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

Substituted Ethers Derived from Ethylene Chlorohydrin^{1,2}

BY SHIRLEY POWELL LINGO WITH HENRY R. HENZE

The chief interest in chloro ethers lies in the ease with which the halogen linked in the α -position can be replaced by other atoms or groups, leading particularly to the formation of cyano ethers, ether amides, ether thioamides, alkoxy acids, alkoxy esters, branched chain aldehydes, alkoxy tertiary alcohols, and keto ethers; the last-mentioned type being capable of conversion into heterocyclic compounds of varying degree of physiological activity and toxicity.

Apparently little consideration has been paid to the feasibility of condensing bifunctional alcohols into substituted α -chloro ethers.³ In this investigation, ethylene chlorohydrin has been condensed, by means of dry hydrogen chloride, with formaldehyde, paraldehyde, propionaldehyde, and *n*-butyraldehyde, respectively. Subsequently, the conversion of these chloro ethers into ether nitriles, and of several of the latter type into keto ethers, has been studied.

The conversion of α -chloro ethers into α -cyano ethers is of considerable interest in that sodium or potassium cyanide, which reacts readily with alkyl halides to form nitriles, are ineffectual and cuprous, mercuric or silver cyanide⁴ must be used; in the latter instance, no isonitrile is formed despite the fact that a carbylamine is usually the chief product of the interaction of silver cyanide and an alkyl halide. As far as we are aware, but one halogenated α -chloro ether has been converted previously into the corresponding halogenated α -cyano ether, the example being α -1,3-dichloroisopropoxypropionitrile.⁵ This very considerable difference in the reactivity of the chlorine atoms linked α - or β - to the oxygen atom in

this chloro ether is characteristic also of the four examples of the new type of monochloroalkoxy nitrile produced in this study.

The ability of the chloroalkoxy nitrile to enter into reaction with Grignard reagents has been tested in the instances of β -chloroethoxyacetone-nitrile and α -(β -chloroethoxy)-propionitrile. In general, the halogen atom shows no tendency to react and ten β -chloroethoxy ketones have been obtained; the one exception was found in the reaction with methylmagnesium iodide, when partial replacement of chlorine by iodine was observed.⁵

These ketones were prepared in the hope that they might serve as intermediates in the synthesis of substituted hydantoins and of quinoline carboxylic acid derivatives. It was disappointing to find that the carbonyl group in this series of keto ethers seems to be not very reactive, and only the 5-isoamyl- and 5-phenyl-5-(2-chloroethoxy)-methylhydantoins and the 5-ethyl- and 5-*n*-propyl-5-[1-(2-chloroethoxy)-ethyl]-hydantoins were obtained readily.

Experimental

Synthesis of the α -Chloro Ethers.—Utilizing the procedure of Henry,³ ethylene chlorohydrin and the appropriate aldehyde were mixed in equimolecular quantities, cooled in an ice-salt bath, and saturated with dry hydrogen chloride. The ether layer was separated, dried over anhydrous calcium chloride; unless the concentration of hydrogen chloride in the chloro ether was maintained, the latter became discolored and partially decomposed. The dried material was freed of dissolved gas by aeration under a partial vacuum of 30–40 mm. All distillations of these compounds were accomplished under diminished pressure, since the chloro ethers exhibit a pronounced tendency to decomposition and formation of resinous products at the temperature of their boiling points at atmospheric pressure.

These chloro ethers are colorless liquids possessed of a faint, pleasant odor when carefully purified, but tend to

(1) Presented before the Division of Organic Chemistry at the 97th meeting of the American Chemical Society at Baltimore, Md., April 3–7, 1939.

(2) Preceding paper in series, Speer with Henze, THIS JOURNAL, 61, 1226 (1939).

(3) Allen with Henze, *ibid.*, 59, 540 (1937).

(4) Gauthier, *Compt. rend.*, 143, 831 (1906).

(5) Cf. ref. 3, page 542, and ref. 2, page 511.