

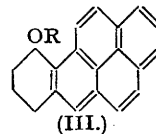
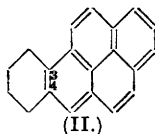
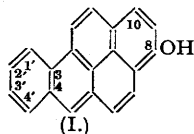
37. *The Direct Hydroxylation of 1' : 2' : 3' : 4'-Tetrahydro-3 : 4-benzpyrene.*

By GEORGE A. R. KON and EDNA M. F. ROE.

Lead tetra-acetate attacks 1' : 2' : 3' : 4'-tetrahydro-3 : 4-benzpyrene almost exclusively in the saturated ring, giving the 1'-acetoxy-compound (III, R = COMe) and a hydrocarbon formulated as 3' : 4'-dihydro-3 : 4-benzpyrene (IV). Acetoxy-derivatives substituted in the pyrene ring system are formed in small amount.

WHEN the carcinogenic hydrocarbon 3 : 4-benzpyrene is injected into rats, a portion of it is excreted in the form of a hydroxylated derivative BPX (Chalmers and Crowfoot, *Biochem. J.*, 1941, **35**, 1270, and previous publications). Evidence that BPX is 8-hydroxy-3 : 4-benzpyrene (I) has been adduced (Berenblum and Schoenthal, *Cancer Res.*, 1943, **3**, 145; Berenblum, Crowfoot, Holiday, and Schoenthal, *ibid.*, p. 151), and it appeared of great interest to attempt to synthesise this compound in view of its bearing on the problem of the mechanism by which carcinogenic compounds are detoxified in the animal body.

A possible route to the desired compound was indicated by the observation of Vollmann, Becker, Corell, and Streeck (*Annalen*, 1937, **531**, 1) that pyrene is first substituted in position 3, but the next substituent enters position 8 or 10; *e.g.*, a mixture of the 3 : 8- and the 3 : 10-quinones is obtained on oxidation. It would therefore be expected that 1' : 2' : 3' : 4'-tetrahydro-3 : 4-benzpyrene (II), which is, in effect, a 3-substituted pyrene, would be further substituted in position 8 or 10. For the introduction of the desired substituent, direct hydroxylation with lead tetra-acetate, which has been frequently used in polycyclic compounds (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1938, **60**, 1893, 2542) appeared to offer an easy route to the tetrahydro-derivatives of the required compounds, which could then be dehydrogenated.



4'-Keto-1' : 2' : 3' : 4'-tetrahydrobenzpyrene (Cook and Hewett, *J.*, 1933, 398; Fieser and Fieser, *J. Amer. Chem. Soc.*, 1935, **57**, 782) affords the hydrocarbon (II) in moderate yield when reduced by the Clemmensen method (*idem, ibid.*; Bachmann, Carmack, and Safir, *ibid.*, 1941, **63**, 1682) and for this reason Fieser and Fieser recommend catalytic reduction at high temperature and pressure in presence of copper chromite; however, an excellent yield of the hydrocarbon has now been obtained by the modified Kishner-Wolff technique (Kon and Soper, *J.*, 1940, 1335). The hydrocarbon has the properties already described by Fieser and Fieser and Bachmann *et al.*, and the higher m. p. quoted by Winterstein, Vetter, and Schön (*Ber.*, 1935, **68**, 1079) could not be confirmed; the compound has been further characterised by means of its trinitrobenzene compound.

Hydroxylation of the hydrocarbon with lead tetra-acetate was tried under a variety of conditions. The separation of the products was tedious, but could be achieved by repeated chromatographic adsorption. The course of the separation could be conveniently observed in ultra-violet light; one of the principal products was a hydrocarbon,  $C_{20}H_{14}$ , with a violet fluorescence, and a more adsorbable fraction with a greenish-blue fluorescence consisted of acetoxy-compounds.

Of the latter, only one could be obtained in reasonable amount for investigation. Hydrolysis by the action of methylmagnesium iodide was not satisfactory, but alkaline hydrolysis readily gave a non-phenolic hydroxy-compound (III, R = H), which was oxidised by the Oppenauer method to the corresponding ketone, m. p. 174—175° depressed by admixture of the 4'-ketone of the same m. p. It is clear that the acetoxy-group must have entered the saturated ring of the hydrocarbon (II), as it does in methylcholanthrene (Fieser and Hershberg, *loc. cit.*, p. 2542); its position on C<sup>1'</sup> was demonstrated by treating the above ketone with methylmagnesium iodide. The product was dehydrated and heated with sulphur, whereby 1'-methyl-3 : 4-benzpyrene was formed; it had m. p. 190—191° and gave a crimson trinitrobenzene compound, m. p. 208—209°, in agreement with the findings of Bachmann and Carmack (*J. Amer. Chem. Soc.*, 1941, **63**, 2494).

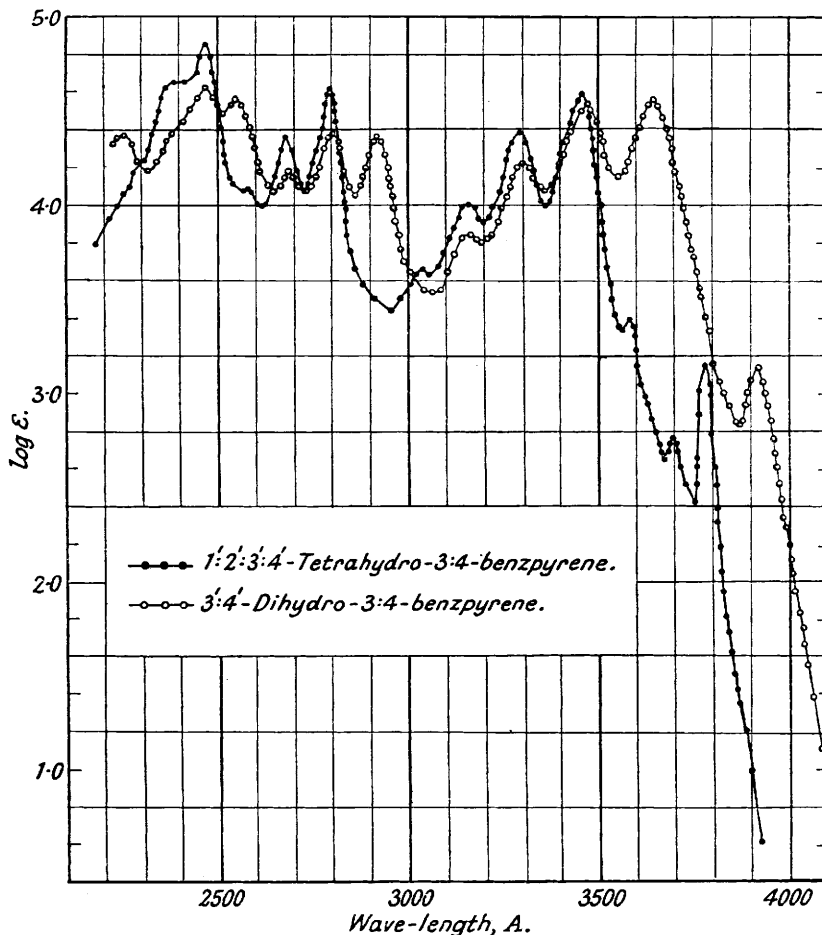
The acetoxy-compound (III, R = Ac) is accompanied by at least two isomerides, m. p.'s 161—162° and 155°, but their formation is uncertain and the amounts formed are always small. At least one of them is a phenolic derivative, because when the crude acetoxylation product containing them was hydrolysed and methylated a methyl ether, m. p. 110—112°, was obtained; this is probably the desired 8(or 10)-methoxy-tetrahydro-3 : 4-benzpyrene.

The hydrocarbon also formed in this reaction can be separated from the small amount of unchanged hydrocarbon (II) by repeated chromatographic adsorption; it melts at 128° and mixtures of it with (II) (m. p. 113°) melt at intermediate temperatures, and the same applies to their trinitrobenzene compounds (m. p. 202—203° and 198—199°, respectively), but there can be little doubt that they are not identical and the new hydrocarbon is a dihydro-3 : 4-benzpyrene isomeric with the compound described as 1' : 2'-dihydro-3 : 4-benzpyrene by Bachmann and Carmack (*ibid.*, p. 1685). Since acetoxylation of tetrahydrobenzpyrene takes place mainly on C<sup>1'</sup>, it seems reasonable to suppose that the new double bond will be introduced between C<sup>1'</sup> and C<sup>3'</sup> with the formation of 3' : 4'-dihydro-3 : 4-benzpyrene (IV). In an endeavour to confirm the structure of this compound,

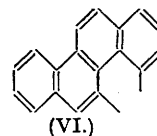
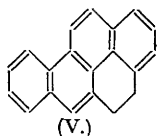
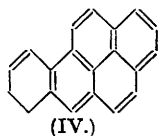
its absorption spectrum and those of tetrahydrobenzpyrene and of Bachmann and Carmack's dihydrobenzpyrene have been measured.

The tetrahydro-compound shows a typical pyrene spectrum (Fig. 1) and requires no comment. Our 3': 4'-dihydro-compound also has a spectrum of the pyrene type (Fig. 1), but the intensities of the principal maxima are reduced and the peaks displaced towards the visible region, an effect compatible with the greater weight of the molecule and the additional double bond in conjugation with those of pyrene. The spectrum of Bachmann and Carmack's compound (Fig. 2) differs appreciably from that of its isomeride and is related to the chrysene rather than the pyrene type of spectrum. In particular, the similarity to the spectrum of 4: 5-di-

FIG. 1.



methylchrysene (VI) (Jones, *ibid.*, p. 313), which is reproduced for comparison, is striking. In the absence of other evidence, this suggests that Bachmann and Carmack's hydrocarbon is more correctly formu-



lated as 6: 7-dihydro-3: 4-benzpyrene (V), which can be regarded as a 4: 5-disubstituted chrysene and is formed by a rearrangement of the double bonds of the expected 1': 2'-dihydro-compound.

Other possible synthetic approaches to the compound BPX have been explored without success, such as the reaction of 3-methoxypyrene with acetyl chloride or succinic anhydride, which gave inseparable mixtures; attempts to introduce a hydroxyl group into 3-acetylpyrene by way of the nitro-compound or by sulphonation were also fruitless.

#### EXPERIMENTAL.

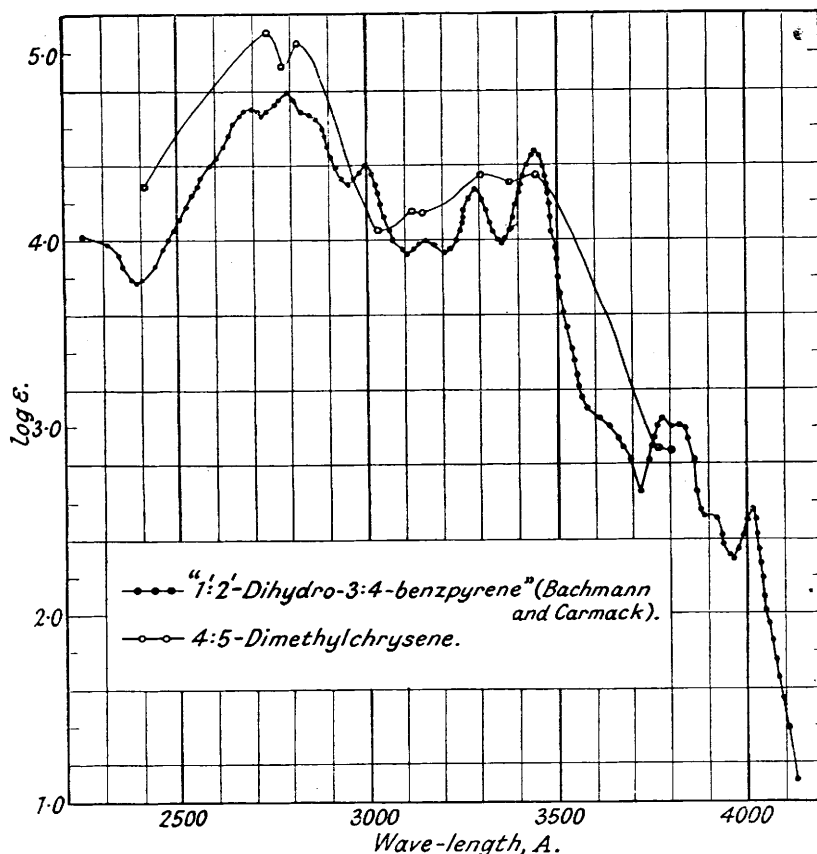
1': 2': 3': 4'-Tetrahydro-3: 4-benzpyrene.—Four sealed tubes, each containing 2 g. of 4'-keto-1': 2': 3': 4'-tetrahydro-3: 4-benzpyrene, 4.5 c.c. of 99% hydrazine hydrate, and 32 c.c. of a 5% solution of sodium in alcohol, were heated

at 200° for 16 hours. The hydrocarbon was extracted with light petroleum (b. p. 60—80°) in which the unchanged ketone is virtually insoluble; the last traces of ketone can be removed by percolating the washed and dried solution through a column of alumina (Spence, type H). The yield of hydrocarbon obtained by evaporation of the solution is 85%, and 7% of unchanged ketone can be recovered. The reduction of the ketone was also successfully carried out on a 20-g. scale in a stainless-steel autoclave of 500 c.c. capacity.\* The trinitrobenzene compound crystallises from benzene-alcohol in orange-red needles, m. p. 198—199° (Found: C, 66.5; H, 4.3.  $C_{28}H_{18}O_6N_3$  requires C, 66.5; H, 4.1%).

7 G. of the hydrocarbon in 32 c.c. of carbon tetrachloride were kept ice-cold and mechanically stirred while 4 g. of chlorosulphonic acid were slowly run in, the stirring being continued for a further 6 hours. After distillation of the solvent, the dark green, gummy material was treated with 30 c.c. of water, and the solution saturated with salt. The dark solid was collected, dried, and added to 30 g. of fused sodium hydroxide (bath at 270° rising to 300° in 10 minutes). The cooled melt was dissolved in water, and the solution repeatedly filtered from a brown amorphous powder. The filtrate was saturated with carbon dioxide, causing a flocculent precipitate, but no definite product could be isolated from it.

*Action of Lead Tetra-acetate.*—This reagent was prepared as described by Dimroth and Schweitzer (*Ber.*, 1923, 56, 1375), recrystallised from acetic acid, and dried in a desiccator. The oxidations were carried out under varying conditions and in different solvents, *viz.*, petroleum, benzene, or mixtures of these. The following is a typical experiment: 10.2 g. of the hydrocarbon in 540 c.c. of "AnalaR" benzene were added to 16.2 g. of lead tetra-acetate suspended in

FIG. 2.



900 c.c. of "AnalaR" acetic acid, the resulting clear brown solution being kept overnight. It was then diluted with much water, the benzene layer separated off, repeatedly shaken with water, finally with sodium carbonate solution, filtered from a sludgy precipitate of lead salts, dried over sodium sulphate, and diluted with its own volume of petroleum (b. p. 60—80°). The solution was percolated through a short, wide column of activated alumina (Spence, type H), which was washed with the same solvent. The colourless solution gave on evaporation a greenish oil which soon solidified. It was dissolved in 1.5 l. of petroleum and percolated through 100 g. of alumina, the column being then washed with 1.5 l. of the same solvent; the petroleum solution gave 3 g. of solid (A) on evaporation. The column was eluted with 3 l. of 1 : 1 petroleum-benzene, which removed 4.5 g. of solid (B). Very little more material was recovered by elution of the column with pure benzene.

(A) was still a mixture melting below 100° and could be resolved by further chromatography in petroleum into unchanged tetrahydrobenzpyrene, which comes through in the first runnings, leaving another hydrocarbon adsorbed on the column. This was eluted with benzene-petroleum and could be purified by way of the picrate, forming brownish-purple needles from benzene-alcohol, m. p. 174—175°, or the trinitrobenzene compound, crimson-red needles from benzene-alcohol, m. p. 202—203° (Found: C, 66.4; H, 3.8.  $C_{28}H_{17}O_6N_3$  requires C, 66.8; H, 3.7%), from which the hydrocarbon (IV) could be regenerated by percolating a benzene solution through alumina. It crystallised from alcohol

\* The authors are greatly indebted to Prof. I. M. Heilbron, D.S.O., F.R.S., for permission to carry out this reduction at the Imperial College of Science and Technology.

in pale buff plates, m. p. 128° (Found: C, 94.3; H, 5.7.  $C_{20}H_{14}$  requires C, 94.4; H, 5.6%), which tend to darken when exposed to light.

The fraction (B) was repeatedly crystallised from alcohol or from acetone-methanol, forming fine, iridescent, flattened needles, m. p. 174—175°, consisting of 1'-acetoxy-1': 2': 3': 4'-tetrahydro-3: 4-benzpyrene (III, R = Ac) (Found: C, 84.2; H, 5.7.  $C_{22}H_{18}O_2$  requires C, 84.0; H, 5.8%). The best yield (70% of material crystallised once) of this compound was obtained when the reaction mixture was kept at room temperature for 20 mins., then warmed for 45 mins. on the steam-bath, the benzene being then distilled off under reduced pressure. The products were isolated by addition of water and extraction with ether; the solid recovered from the extract was finally chromatographed in benzene-petroleum and crystallised from acetone-methanol.

*Isomeric Acetoxy-compounds.*—By a tedious fractional crystallisation from alcohol, ethyl acetate, or petroleum, these were isolated in small amounts in acetoxylation experiments performed at room temperature. One of these compounds forms colourless iridescent plates which look pale green in ordinary light owing to their intense fluorescence, which is blue in ultra-violet light, and melt at 161—163° (Found: C, 84.2; H, 6.0.  $C_{22}H_{18}O_2$  requires C, 84.0; H, 5.8%). Another compound isolated in very small amount has a green fluorescence in ultra-violet light and melts at about 155° (Found: C, 84.3; H, 5.8%); it is more strongly adsorbed on alumina than the isomeride of m. p. 161—163°.

*x-Methoxy-1': 2': 3': 4'-tetrahydro-3: 4-benzpyrene.*—The crude mixture of acetoxy-compounds (0.4 g.) obtained by eluting the column of alumina with benzene after removal of the hydrocarbons (cf. p. 145) was boiled with 2 g. of potassium hydroxide, 2 c.c. of water, and 40 c.c. of methyl-alcohol for an hour, cooled, treated with an excess of methyl sulphate, and the process repeated several times. The excess of reagent was finally hydrolysed with more alkali, and the product isolated by dilution with water was recrystallised from alcohol. The solid obtained after repeated crystallisation was the acetoxy-compound, m. p. 155°; the mother-liquors deposited a compound with a similar green fluorescence, but melting at 110—112° after repeated crystallisation from ethyl acetate-alcohol, evidently the *methoxy*-compound (Found: C, 88.4; H, 6.5.  $C_{21}H_{16}O$  requires C, 88.1; H, 6.3%).

*1'-Hydroxy-1': 2': 3': 4'-tetrahydro-3: 4-benzpyrene* (III, R = H).—2 G. of the acetoxy-compound, m. p. 174—175°, were boiled with 7 g. of potassium hydroxide and 150 c.c. of alcohol, 20 c.c. of water being gradually added to the solution in the course of 45 mins. The bulk of the alcohol was then distilled off, and more water added. The *hydroxy*-compound (1.5 g.) was collected and recrystallised from alcohol, forming thick prisms, m. p. 180—181° (Found: C, 88.1; H, 6.1.  $C_{20}H_{16}O$  requires C, 88.2; H, 5.9%).

*1'-Keto-1': 2': 3': 4'-tetrahydro-3: 4-benzpyrene.*—2.65 G. of crude hydroxy-compound, 25 c.c. of cyclohexanone, 135 c.c. of benzene, and 9 g. of aluminium *tert.*-butoxide were boiled for 16 hours under reflux. The product was isolated by washing the benzene solution with dilute acid, drying, diluting with its own volume of petroleum (b. p. 60—80°), and percolating it through a column of alumina. Some difficulty was experienced owing to the presence of cyclohexanone and its condensation products in the eluate, but these were distilled off in a high vacuum after evaporation of the solvent. The *ketone* crystallised from benzene-petroleum and from ethyl acetate-alcohol in sulphur-yellow plates, m. p. 174—175°, depressed by admixture of the 4'-ketone (Found: C, 88.8; H, 5.3.  $C_{20}H_{14}O$  requires C, 88.9; H, 5.2%).

*1'-Methyl-3: 4-benzpyrene.*—0.6 G. of the ketone was added to a Grignard reagent prepared from 0.2 g. of magnesium, 1.5 c.c. of methyl iodide, and 15 c.c. of ether, the mixture being boiled under reflux for 5 hours. It was decomposed with ice and dilute hydrochloric acid, the ethereal solution washed, dried, and evaporated. The residue was heated for 6 hours to 130—150° at a pressure of 0.5 mm., the formation of a crystalline sublimate being observed. 0.1 G. of sulphur was now added, and the whole heated to 230—240° for 30 minutes, evolution of hydrogen sulphide then having ceased. On distillation in a high vacuum a hard solid was obtained, apparently in very good yield. It was dissolved in benzene and treated with an excess of picric acid, the resulting dark reddish-brown picrate being once recrystallised from benzene; m. p. 182—183°. The *hydrocarbon* was regenerated by percolating a benzene solution of the picrate through a column of alumina, and crystallised from benzene-alcohol in pale yellow plates, m. p. 190—191° (Found: C, 94.6; H, 5.4.  $C_{21}H_{14}$  requires C, 94.7; H, 5.3%). The trinitrobenzene compound formed crimson needles, m. p. 208—209°.

*1': 2'-Dihydro-3: 4-benzpyrene* (V?).—This was prepared as described by Bachmann and Carmack (*loc. cit.*, p. 1685); the best product was obtained by decomposition of the pyridinium salt isolated by them, and was purified by sublimation in a high vacuum and crystallisation from benzene-alcohol. It formed plates, m. p. 148—149°, unchanged by further crystallisation. The trinitrobenzene compound formed dark orange needles, m. p. 199—200°, after crystallisation from benzene-alcohol (Found: C, 67.3; H, 3.9.  $C_{26}H_{17}O_6N_3$  requires C, 66.8; H, 3.7%). Mixtures of this compound with the trinitrobenzene compounds of tetrahydro- and the isomeric dihydro-benzpyrene melt at intermediate temperatures.

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THE CHESTER BEATTY RESEARCH INSTITUTE,  
THE ROYAL CANCER HOSPITAL (FREE), LONDON, S.W.3.

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