empirical formula: $C_{5.35}H_{8.36}N_{1.0}O_{1.55}$, or an approximate $(C_{10}H_{16}N_2O_3)_x$.

This value for nitrogen is confirmed by the analysis of several purified samples from which prolonged extraction failed to remove any more rubber. These, when corrected for ash content, gave by titration 12% of nitrogen. A critical examination of the work of previous investigators also indicates 12% as their best value for nitrogen. These observations are stressed because of the still prevalent practice, particularly in stating the results of the analysis of rubber, of multiplying the nitrogen content by 6.25 to compute the protein content of the material, which of course arbitrarily assumes the nitrogen content of a protein to be 16%.

Hydrolysis of the purified protein material was obtained by treating 11 g. of it with 100 cc. of dilute sulfuric acid (40 cc. of concd. acid to 140 cc. of water), boiling under reflux. The hydrolyzate was filtered to remove 3.18 g. of humin, whose nitrogen content was found to be 0.7%. This humin was treated with benzene, which removed about one-half of it. From the benzene solution, alcohol precipitated a substance which had all the appearances of rubber. Making the assumption that this material was rubber, it is possible to recompute the analysis result of the protein, and to find that the nitrogen content would be somewhere between 15 and 16%, which is the nitrogen content generally expected in a protein. It should, however, be repeated that removal of the last rubber by solvents was found impossible before completion of the hydrolysis.

The hydrolyzate was separated into its constituents by the carbamate method,[6] as more recently improved.[7] The dibasic amino acids were isolated and separated by the method of Block.[8]

When needed, final identification was obtained by preparing crystalline derivatives, according to the procedure of Crosby and Kirk[9] and comparing them with the published photomicrographs. The picrates were used to characterize glycine, leucine, and proline, and the flavianate to identify aspartic acid and leucine.

The amino acids found and definitely identified were: glycine, aspartic acid, leucine, proline, arginine, histidine, lysine and representative of the group comprising alanine, phenylalanine, hydroxyproline and serine. This group was not investigated further. The amino acids which were definitely absent included cystine, tyrosine and glutamic acid.

Summary

The protein constituent of rubber has been extracted from the natural rubber by removal of the rubber hydrocarbon with solvents, followed by electrodialysis of the residue. This material has been analyzed, subjected to hydrolysis, and its amino acid constituents have been separated and identified.

(6) Kingston and Schryver, *Biochem. J.*, **18** [5], 1070 (1924).
(7) Caldwell and Rose, *J. Biol. Chem.*, **107**, 45 (1934).
(8) Block, *ibid.*, **106**, 457 (1934).
(9) Crosby and Kirk, *Mikrochemie*, **18**, 137 (1935).

THE MIDGLEY FOUNDATION
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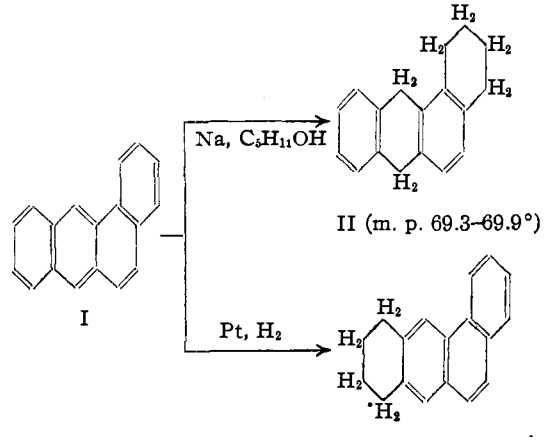
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Reduction and Hydrogenation of Compounds of the 1,2-Benzanthracene Series

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

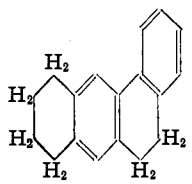
The investigation of the reduction and hydrogenation of carcinogenic hydrocarbons of the 1,2-benzanthracene series is of interest both because of the possibility of obtaining in this way new compounds of value in further defining the limits of carcinogenic activity and because a knowledge of the center, or centers, of chemical reactivity in the molecule of an active carcinogen may be of value in understanding the biological actions of the compound. The recent development of a convenient synthesis of 1′,2′,3′,4′-tetrahydro-1,2-benz-10-anthrone[2] (VI, below) made available a starting material for the preparation of new reference compounds of known structure and provided the occasion for the present work.

With 1,2-benzanthracene itself we have been able to establish that reduction with sodium and amyl alcohol, and by low pressure hydrogenation, proceeds as indicated in formulas II and III, respectively. The first reaction gave a nicely

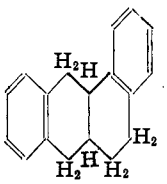


(1) Lilly Research Fellow.
(2) Fieser and Hershberg, THIS JOURNAL, **59**, 2331 (1937).

crystalline hexahydro derivative which does not form molecular compounds with picric acid or trinitrobenzene, from which it may be inferred that the two remaining aromatic rings are separated by at least one hydroaromatic nucleus. Of the three possible formulas, II, IV, and V, the second (IV) is that of a hydrocarbon synthesized

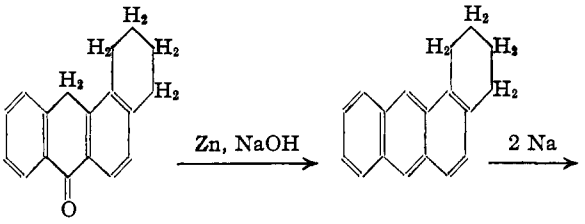


IV (oil)

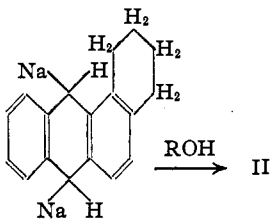


V (unknown)

by Burger and Mosettig[3] and found to be an oil, thus differing from our compound, and it was possible to distinguish between formulas II and V by the preparation of the hydrocarbon in question in a different way. By reduction with zinc and alkali, the synthetic tetrahydro-1,2-benz-10-anthrone VI was converted into the new 1′,2′,3′,4′-tetrahydro-1,2-benzanthracene (VII),



VI VII (m. p. 104.5–105°)



VIII

and from this a dihydro derivative, presumably the *meso*-dihydride, was obtained by the addition of sodium and alcoholysis of the product, a reaction developed by Schlenk and co-workers[4] and applied recently by Bachmann[5] to the preparation of *meso*-dihydromethylcholanthrene. The hexahydride thus obtained was identical with that resulting from the action of sodium and amyl alcohol on 1,2-benzanthracene, which definitely proves that four of the added hydrogen atoms are situated in the angular ring. This evidence excludes both of the formulas IV and V and, since II represents the only other structure consistent with the failure of the hydrocarbon to form a picrate, the two remaining hydrogens are definitely located in the *meso*-positions, as inferred from the second method of preparation.

Using Adams catalyst, in combination with ferrous chloride[6] and hydrochloric acid[7] as activators, it was found that 1,2-benzanthracene can be reduced rapidly and in good yield to a crystalline tetrahydro derivative different from the synthetic 1′,2′,3′,4′-tetrahydride (VII) described above. The only other structure consistent with the fact that the substance is an entirely stable compound is that of the 5,6,7,8-tetrahydride, formula III, and indeed our material corresponds exactly in melting point and in that of its picrate with a hydrocarbon of this structure synthesized by Cook and Hewett.[8] Hydrogenation at low pressure therefore leads, in the first recognized stage, to the saturation of the terminal ring of the anthracene part of the molecule, and there is no indication that the *meso*-dihydride is an intermediate product. The further hydrogenation was studied only in one trial experiment in which the reaction was interrupted with the absorption of three moles of hydrogen. The product seemed to be a mixture, and it was investigated only to the extent of ascertaining that it did not consist in large part of the 3,4,5,6,7,8-hexahydride (IV) of Burger and Mosettig.[3]

The reactions of 10-methyl-1,2-benzanthracene[9] are of particular interest because of the carcinogenic properties of this hydrocarbon.[10]

(3) Burger and Mosettig, THIS JOURNAL, **59**, 1302 (1937).

(4) Schlenk, Appenrodt, Michael and Thal, *Ber.*, **47**, 473 (1914).

(5) Bachmann, *J. Org. Chem.*, **1**, 347 (1936).

(6) Carothers with Adams, THIS JOURNAL, **45**, 1071 (1923); **47**, 1047 (1925).

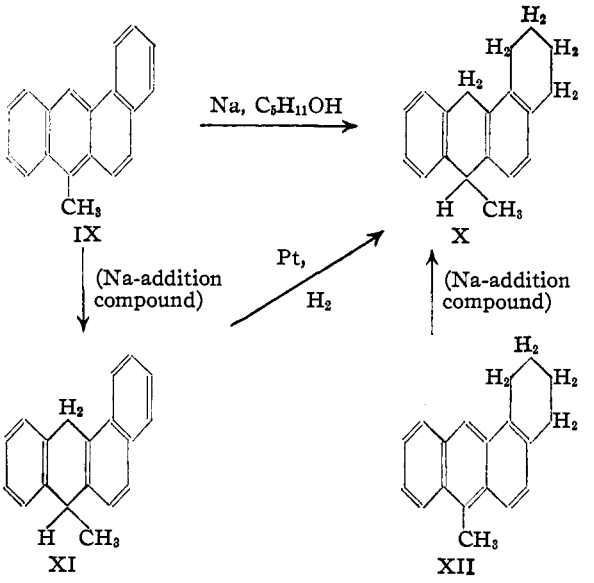
(7) Brown, Durand and Marvel, *ibid.*, **58**, 1594 (1936).

(8) Cook and Hewett, *J. Chem. Soc.*, 365 (1934).

(9) (a) Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936); (b) Fieser and Hershberg, *ibid.*, **59**, 1028 (1937); (c) Cook, *J. Chem. Soc.*, 393 (1937).

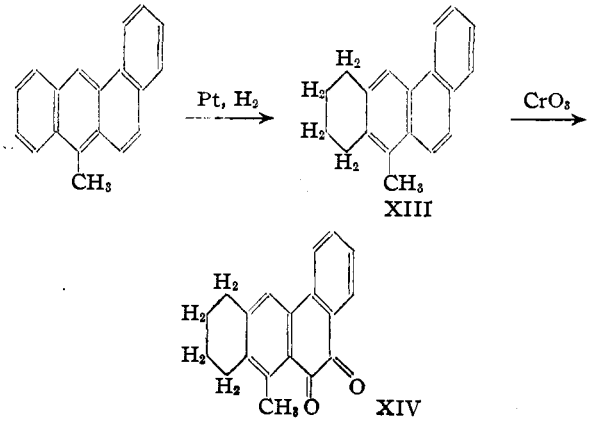
(10) The report by Cook, Robinson and Goulden, *J. Chem. Soc.*, 393 (1937), that their specimen of 10-methyl-1,2-benzanthracene had produced no tumors in mice after one hundred and thirty days does not, as their statement of the case implies, contradict the results of Shear [see Fieser, *et al.*, *Am. J. Cancer*, **29**, 260 (1937)]. Using a sample of the hydrocarbon synthesized by Fieser and Newman,[9a] Shear had obtained 15 tumors in 20 mice in four months, but the experiment differed from that of the English workers in that he employed the injection technique, whereas it became evident later that they had applied the hydrocarbon to the skin in 0.3% benzene solution twice weekly. Cook and co-workers did not mention this significant difference in the method of administration or even specify at the time the method employed in their tests, and readers not familiar with their usual practice in this detail of the assay were left to infer either that the biological results from the two laboratories were definitely discordant or that there were significant differences in the samples of hydrocarbon submitted to assay. In a later publication by Bachmann, Cook, *et al.*, *Proc. Roy. Soc.* (London),

Reduction with sodium and amyl alcohol again gave a hexahydro compound. This hydrocarbon could not be caused to crystallize at 2–4° and it formed no picrate, but the structure was fully established as that of 1′,2′,3′,4′,9,10-hexahydro-10-methyl-1,2-benzanthracene (X) by the preparation of the compound in two other ways. In the first process 10-methyl-1,2-benzanthracene was first converted into the *meso*-dihydro derivative (XI) by the alcoholysis of the disodium compound; the position of the added hydrogens being definitely established by the observation that the hydrocarbon yields 1,2-benzanthraquinone on oxidation. On hydrogenation in the presence of Adams catalyst and a promoter, the dihydride gave a hexahydride identical (see below) with that obtained directly from the fully aromatic hydrocarbon, which shows that two of the hydrogen atoms of the hydroaromatic compound are located in the *meso*-positions. As starting material for the next method of preparation we employed the new hydrocarbon 1′,2′,3′,4′-tetrahydro-10-



methyl-1,2-benzanthracene, XII, which was synthesized from the known tetrahydro-1,2-benz-10-anthrone VI by the Grignard reaction and dehydration. Alcoholysis of the disodium compound of XII gave the same hexahydride as obtained by the other two methods; therefore the remaining four hydrogens are located in the angular ring and the structure X is fully established. For the identification of the three samples of the liquid hydrocarbon, each sample was analyzed and submitted to oxidation. In each case the oxidation product was 1′,2′,3′,4′-tetrahydro-1,2-benzanthraquinone, identified by comparison with a sample of synthetic material.[2]

The catalytic hydrogenation of 10-methyl-1,2-benzanthracene (Adams catalyst, promoter) proceeded exactly as with the parent hydrocarbon, the terminal anthracene ring being the first detectable point of attack. The structure of the crystalline 5,6,7,8-tetrahydride (XIII) follows

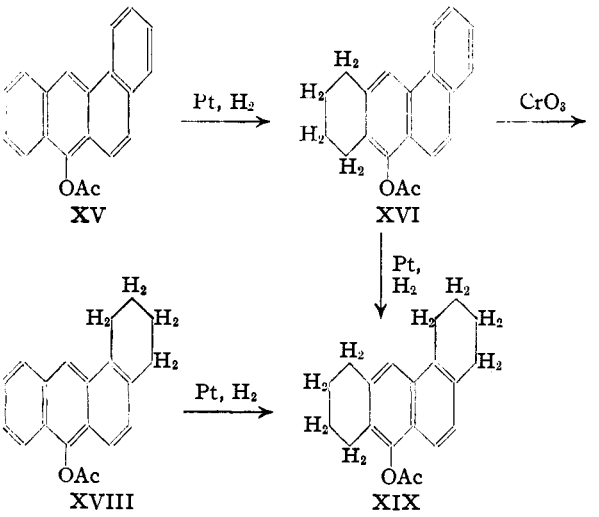


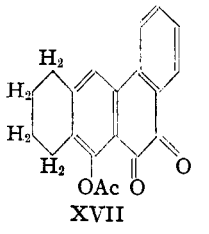
123B, 343 (1937), the test method is recorded and it is stated that, although most of the mice were lost as the result of an epidemic, the application of 10-methyl-1,2-benzanthracene to the skin appeared to result in the slow production of at least a few tumors. Following the appearance of the paper by Cook, Robinson and Goulden, Dr. Shear repeated the earlier experiment and also initiated painting tests. He reports that within three months after the subcutaneous injection of the crystalline hydrocarbon, tumors were obtained in 5 of 10 Strain A mice, the first two tumors appearing on the sixty-sixth day. In another experiment the hydrocarbon was applied in 0.3% benzene solution thrice weekly to the skin of 20 Strain A mice; in this series no tumors appeared in the first four months, while at the end of the fifth month 6 of 17 surviving animals had papillomas. There seems to be no discordance in the results thus far obtained in the two laboratories and the observations point to the interesting conclusion that the rate of tumor production is more dependent on the method of administration in the case of the 10-methyl compound than with other hydrocarbons for which data have been published. As far as can be judged from the data on hand for methylcholanthrene, cholanthrene, 1,2,5,6-dibenzanthracene, and 3,4-benzpyrene, the average time of the appearance of tumors in mice is about the same whether these hydrocarbons are administered by application to the skin or by injection of the crystals. It is already evident that with 10-methyl-1,2-benzanthracene there is a considerably greater spread in the rate of production of sarcomas and of epitheliomas, and recent results of Dr. Shear indicate that this peculiarity probably is characteristic also of the 5-methyl isomer. By the injection method he obtained 18 tumors in 20 mice in eight months, and half of the animals had tumors by the end of the sixth month, while in the painting experimeuts with this hydrocarbon reported by Bachmann, Cook, *et al.* (*loc. cit.*) the average time of the appearance of tumors was nearly twice as long. On the present evidence 10-methyl-1,2-benzanthracene produces sarcomas about twice as rapidly as the 5-isomer and is comparable with cholanthrene in sarcoma-producing power. We stressed the latter comparison in earlier publications at a time when results of painting experiments were not yet available, but from a consideration of all criteria of activity now on record it appears that the 10-methyl compound is somewhat inferior to cholanthrene in general carcinogenic properties, for, although equally potent in certain respects, it falls short of cholanthrene in the rapidity with which it produces epitheliomas when applied to the skin. 10-Ethyl-1,2-benzanthracene[9b] produces sarcomas more slowly than the 10-methyl compound, Dr. Shear having obtained 13 tumors in 20 mice in nine months, using the injection technique.

from the fact that it behaves like a phenanthrene derivative, giving on oxidation a quinone which forms a quinoxaline derivative and which therefore is an *o*-phenanthrenequinone, XIV.

Schroeter[11] was inclined to regard the *meso*-dihydro derivatives of anthracene and phenanthrene as necessary intermediates in the conversion of these hydrocarbons by catalytic hydrogenation into the 1,2,3,4-tetrahydrides, for he found that the dihydrides are often formed in considerable quantity in the early stages of the reaction and that they can be converted in part into the *as*-tetrahydrides on further hydrogenation. Fries,[12] however, found that with other catalysts anthracene yields chiefly the *as*-tetrahydride and very little of the *meso*-dihydride, and that the further hydrogenation of the latter hydrocarbon is a much slower reaction than the formation of the *as*-tetrahydride directly from anthracene under similar conditions. Recent studies of the hydrogenation of phenanthrene[13] have further indicated the importance of the catalyst in determining the course of the reaction, and it seems probable that in most cases at least the di- and tetrahydrides of the tricyclic hydrocarbons are formed in independent reactions, which may or may not be concurrent. Our results with the tetracyclic hydrocarbons point in the same direction, and in the case of the 10-methyl compound the intermediate formation of the *meso*-dihydride under the conditions employed seems definitely excluded. When 10-methyl-1,2-benzanthracene was allowed to absorb just one mole of hydrogen, the product was a mixture of starting material and the tetrahydride, XIII. Of still greater significance is the observation, cited above, that *meso*-dihydro-10-methyl-1,2-benzanthracene (XI) is not converted on catalytic hydrogenation into the 5,6, 7,8-tetrahydride but yields the hexahydride, X.

The catalytic hydrogenation of 1,2-benzanthranyl-10-acetate, XV, was found to proceed in the first step exactly as with the two compounds above, the 5,6,7,8-tetrahydro compound, XVI, being obtained in 77% yield. The structure follows from the formation of an *o*-phenanthrenequinone (quinoxaline derivative) on oxidation. When the hydrogenation of XV was continued until four moles of hydrogen had been absorbed, there was isolated in fair yield a crystalline product which was found to be the 1′,2′,3′,4′,5,6,7,8-octahydride, XIX, the evidence being that an identical compound was obtained by the hydrogenation of synthetic 1′,2′,3′,4′-tetrahydro-1,2-benzanthranyl-10-acetate (XVIII). This octahydride results from the saturation of the terminal rings of the anthracene and the phenanthrene systems present in the starting material, XV, and can be obtained from either of the tetrahydrides; the end ring of the anthracene system is the more easily reduced of the two.





That 1,2-benzanthranyl-10-acetate is hydrogenated in a ring adjacent to that which is hydroxylated, finds a correlation in the observation of Brown, Durand and Marvel[7] that both α- and β-naphthol are reduced under similar conditions to *ar*-tetrahydro compounds. Even with the phenanthrene derivative XVI, the entering hydrogen atoms avoid entrance of the hydroxylated nucleus.

Whereas 1′,2′,3′,4′-tetrahydro-1,2-benz-10-anthrone (VI) yields 1′,2′,3′,4′-tetrahydro-1,2-benzanthracene when reduced with zinc and alkali, it is of interest that the reduction of the enol acetate XVIII with zinc and ammonia proceeds beyond the anthracene stage and gives 1′,2′,3′,4′,-9,10-hexahydro-1,2-benzanthracene (II), identical with that obtained by the two methods already described.

The catalytic hydrogenation of methylcholan-

(11) Schroeter, *Ber.*, **57**, 2003 (1924); **57**, 2025 (1924); Schroeter, Müller and Huang, *ibid.*, **62**, 645 (1929).

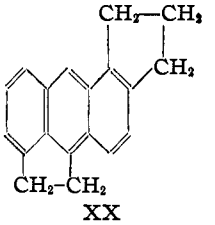
(12) Fries and Schilling, *ibid.*, **65**, 1494 (1932); Fries, Walter and Schilling, *Ann.*, **516**, 248 (1935).

(13) Burger and Mosettig, THIS JOURNAL, **57**, 2731 (1935); **58**, 1857 (1936); Durland and Adkins, *ibid.*, **59**, 135 (1937).

threne proceeds less smoothly than with the compounds carrying no substituents in the end anthracene ring and we are making a separate study of this reaction. The hexahydromethylcholanthrene of Wieland and Dane[14] has been encountered as one hydrogenation product and its structure is under investigation. As a corollary to the reduction studies, we are investigating the oxidation of carcinogenic hydrocarbons and related substances with lead tetraacetate, having found that 1,2-benzanthracene can be converted by this reagent into 1,2-benz-10-anthranyl acetate in fairly good yield.

Attention may be called to the striking difference in the point of primary attack in the reactions of 1,2-benzanthracene and 10-methyl-1,2-benzanthracene with sodium and with catalytically activated hydrogen. The sodium reaction probably reveals the true centers of greatest energy accumulation in the molecule, but in the catalytic reaction these active centers at the *meso* carbon atoms are left undisturbed and the attachment of hydrogen occurs at a terminal, benzenoid nucleus which is more stable, in the chemical sense, than the central anthracene ring. It may be significant that there is some correlation between the course of the hydrogenation of these anthracene derivatives and the observation of Boyland and Levi[15] that in the process of metabolism anthracene is attacked in a terminal, rather than the central, ring.

The present work makes available for biological tests four hydroaromatic derivatives of the carcinogenically active[10] 10-methyl-1,2-benzanthracene, namely, the 9,10-dihydride, the 1′,2′,3′,4′- and 5,6,7,8-tetrahydrides, and the 1′,2′,3′,4′,9,10-hexahydride, and tests with these hydrocarbons are being conducted by Dr. M. J. Shear. We may point out that the synthesis of the 5,6,7,8-tetrahydride (XIII) represents a logical step in our investigation of the limiting features of structure associated with carcinogenic activity. 10-Methyl-1,2-benzanthracene is the simplest benzanthracene which has been found to produce sarcomas with considerable rapidity and regularity. To determine if the angular aromatic ring is essential to the activity, we synthesized 1,2-cyclopenteno-5,10-aceanthrene[16] (XX) for comparison with cholanthrene, and Dr. Shear has since obtained tumors at the site of injection in three of twenty mice within ten months after the injection of a lard solution of XX; one of the



XX

three mice was a male. As a next step it seemed desirable to evaluate the importance of the terminal ring of the anthracene system, and it will be seen that the new hydrocarbon, XIII, in which this ring is replaced by a hydroaromatic ring, has a structure fulfilling these requirements. We are undertaking the synthesis of similarly substituted phenanthrene derivatives in which a possible reversion to the benzanthracene structure in the organism is eliminated.

Attention may be called to two points of technique. In characterizing or purifying some of the hydrocarbons described in this work we were impressed with the general superiority of the trinitrobenzene complexes as compared with the picrates, and for the recovery of hydrocarbons from their trinitrobenzene or picric acid complexes we employed to great advantage the method of chromatographic adsorption. This application of the adsorption technique has been employed also by Plattner and St. Pfau,[17] whose paper reached us subsequently to the development of the method in this Laboratory.

Experimental Part[18]

Preparation of 1,2-Benzanthracene.—Following Bachmann,[5] 6 g. of α-naphthyl *o*-tolyl ketone was mixed with 2 g. of zinc dust and pyrolyzed at 400–410° for three hours. Purification by distillation and passage through a tower of alumina in benzene solution gave a total of 2.75 g. of colorless hydrocarbon, m. p. 159.5–160.5°, and 0.6 g. of yellow product, m. p. 159–160°; total yield, 61%.

Since Bachmann reported no comparison experiment to test the effectiveness of zinc, we investigated the pyrolysis of the ketone alone at the same temperature and found that in this case the reaction proceeded only very slowly. The addition of zinc caused a prompt acceleration. It is of interest that in the first example of the reaction attributed to Elbs, Behr and van Dorp[19] obtained anthracene by distilling *o*-tolyl phenyl ketone over zinc dust in a hot tube.

5,6,7,8-Tetrahydro-1,2-benzanthracene (III).—In a typical experiment 0.5 g. of 1,2-benzanthracene in 150 cc. of

(14) Wieland and Dane, *Z. physiol. Chem.*, **219**, 240 (1933).

(15) Boyland and Levi, *Biochem. J.*, **29**, 2679 (1935); **30**, 728 (1936); **30**, 1225 (1936).

(16) Fieser and Hershberg, THIS JOURNAL, **59**, 394 (1937).

(17) Plattner and St. Pfau, *Helv. Chim. Acta*, **20**, 224 (1937).

(18) All melting points are corrected. Analyses by Mrs. G. M. Wellwood and Mrs. Verna R. Keevil.

(19) Behr and van Dorp, *Ber.*, **6**, 753 (1873); **7**, 16 (1874).

absolute alcohol, with 50 mg. of Adams catalyst[20] and a promoter consisting of 0.2 cc. of a 1% solution of ferrous chloride in dilute hydrochloric acid (10 cc. of concentrated acid in 90 cc. of water), absorbed 2 moles of hydrogen in four hours. The catalyst was removed by adding Norite and filtering, and after concentrating the solution and adding 0.7 g. of trinitrobenzene, 0.7 g. (77%) of the addition compound, 159–160°, separated on cooling. Recrystallized from alcohol, the complex formed lemon-yellow needles, m. p. 159.5–160.5°.

Anal. Calcd. for $C_{18}H_{16}\cdot C_6H_3O_6N_3$: N, 9.44. Found: N, 9.81.

The hydrocarbon isolated as such in another experiment formed colorless, flat needles from methanol and melted at 88.5–89.5°. The picrate formed orange needles, m. p. 156.5–157.5°, from methanol. For the synthetic hydrocarbon and its picrate Cook and Hewett[8] report the melting points 89–90° and 155° (uncorr.?), respectively.

It was our experience, at least in a limited number of trials, that the ferrous chloride solution is definitely effective in promoting the hydrogenation. With catalyst prepared from pure ammonium chloroplatinate no reduction occurred (four additions of catalyst) until iron salt was added and it then proceeded rapidly.

1',2',3',4'-Tetrahydro-1,2-benzanthracene (VII).—Using Martin's procedure,[21] 3 g. of 1',2',3',4'-tetrahydro-1,2-benz-10-anthrone[2] in 50 cc. of toluene was reduced with 10 g. of zinc dust (activated with 50 mg. of copper sulfate) and 180 cc. of 2 *N* sodium hydroxide, added in portions while refluxing for eighteen hours. The separated toluene layer was passed through a tower of alumina and evaporated and the residue was treated in methanol with 3 g. of picric acid, giving 1.6 g. (32%) picrate, m. p. 144–144.5°. Recovery of the hydrocarbon was accomplished by passing a benzene solution of the picrate through a tower of alumina, when all of the picric acid was adsorbed in a narrow zone and the hydrocarbon passed into the filtrate. On crystallizing from methanol the material recovered from the filtrate, there was obtained 0.62 g. of hydrocarbon, m. p. 103–104°, and 0.12 g., m. p. 102–103° (26%). After repeating the process of conversion to the picrate, recovery by adsorption, and crystallization, the hydrocarbon formed flat blades having a brilliant blue fluorescence, m. p. 104.5–105°. The picrate crystallizes from methanol as brownish red needles, m. p. 147.5–148°.

Anal. Calcd. for $C_{18}H_{16}$: C, 93.07; H, 6.93. Found: C, 93.35; H, 6.86. Picrate, calcd. for $C_{18}H_{16}\cdot C_6H_3O_7N_3$: N, 9.11. Found: N, 9.26.

1',2',3',4',9,10-Hexahydro-1,2-benzanthracene (II). (a) **From 1,2-Benzanthracene.**—To a refluxing solution of 1 g. of colorless 1,2-benzanthracene in 150 cc. of isoamyl alcohol 8 g. of sodium was added in the course of three and one-half hours. Water was added cautiously to the cooled solution under reflux, and the organic layer was diluted with ether and washed repeatedly with water and dilute acid. After removal of the solvent the residue was distilled at 2 mm. and crystallized from methanol; yield, 0.55 g. (53%), m. p. 69–71°. Recrystallization from methanol gave iridescent plates, m. p. 69.3–69.9°. Neither picric acid nor trinitrobenzene gave addition compounds.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.27; H, 7.74. Found: C, 92.16; H, 7.94.

(b) **From the 1',2',3',4'-Tetrahydride.**—To 0.4 g. of sodium, powdered by stirring under xylene in a nitrogen atmosphere and washed with benzene, a solution of 0.2 g. of 1',2',3',4'-tetrahydro-1,2-benzanthracene in 15 cc. of benzene and 15 cc. of ether was added. On stirring the mixture for twenty-four hours under a positive pressure of nitrogen, the solution, at first blue-green, became purple and the sodium gradually agglomerated. There seems to be no advantage in the use of powdered metal, and with a good stirrer (wire) the reaction probably is complete in a much shorter time than that allowed. After treatment with alcohol and recovery as in Bachmann's[5] procedure there was obtained 0.15 g. (74%) of hydrocarbon melting at 68.8–69.8° and identical (mixed m. p.) with that above (a).

(c) **From 1',2',3',4'-Tetrahydro-1,2-benzanthranyl-10-acetate (XVIII).**—When the acetate (1 g.) was warmed on the steam-bath with zinc dust (6 g.) and 15% ammonia solution (30 cc.) little change occurred until toluene (15 cc.) was added. Concentrated ammonia solution (300 cc.) was then added in portions under reflux during two days. The toluene was separated from the cooled mixture, the solid was collected, dried in vacuum, and extracted with benzene. The combined toluene and benzene solutions were passed through a tower of alumina. The small amount of hydrocarbon present readily passed into the filtrate (blue fluorescence), while the bulk of the material was adsorbed (yellow fluorescence) and eliminated. The residue from the evaporated filtrate yielded 0.13 g. (15%) of plates, m. p. 67–69°, from methanol, and after further purification the sample melted at 69.2–69.7° and gave no depression with the material above (a).

5,6,7,8-Tetrahydro-10-methyl-1,2-benzanthracene (XIII).—A solution of 1 g. of 10-methyl-1,2-benzanthracene in 200 cc. of absolute alcohol with 0.2 g. of Adams catalyst and one drop of concentrated hydrochloric acid absorbed 2 moles of hydrogen in four hours. The once crystallized product, m. p. 72.5–73.5°, was obtained in yield of 0.58 g. (57%). Two more crystallizations from methanol gave glistening leaflets, m. p. 73.9–74.4°, showing a purple-blue fluorescence in ultraviolet light. The picrate crystallizes from methanol as slender, orange needles, m. p. 186–187°.

Anal. Calcd. for $C_{19}H_{18}$: C, 92.65; H, 7.36. Found: C, 93.05; H, 7.49. Picrate, calcd. for $C_{19}H_{18}\cdot C_6H_3O_7N_3$: N, 8.84. Found: N, 9.16.

Quinoxaline Derivative of 5,6,7,8-Tetrahydro-10-methyl-1,2-benz-3,4-anthraquinone (XIV).—A solution of 160 mg. of the tetrahydride, XIII, in 10 cc. of warm glacial acetic acid was treated with 150 mg. of chromic anhydride in acetic acid, heated at 60° for one-half hour, and refluxed for one hour. Diluted with water and cooled, the solution deposited 20 mg. of crystalline quinone. This was converted directly to the quinoxaline derivative by short boiling in glacial acetic acid solution with 10 mg. of *o*-phenylenediamine. Crystallized from glacial acetic acid, the compound formed bright yellow microcrystals, m. p. 162–164°.

(20) The catalyst contained 1–2% of palladium, dissolved with the platinum in the aqua regia; it absorbed twice as much hydrogen as samples prepared from the same platinum but containing no palladium, and it was considerably more active.

(21) Martin, THIS JOURNAL, **58**, 1438 (1936).

Anal. Calcd. for $C_{25}H_{20}N_2$; C, 86.17; H, 5.79. Found: C, 85.82; H, 5.83.

1',2',3',4'-Tetrahydro-10-methyl-1,2-benzanthracene (XII).—This was synthesized from the anthrone VI (3.3 g.) and methylmagnesium chloride in the usual manner,[9b] purified with the use of an adsorption tower, and crystallized from methanol, the yield of material melting at 115–118° being 2.25 g. (68%). Further crystallization gave pale yellow, thin, flat needles having a brilliant blue fluorescence by daylight, m. p. 117.3–117.8°. The picrate forms cottony clusters of fine, dark brown needles, m. p. 161–162°.

Anal. Calcd. for $C_{19}H_{18}$: C, 92.65: H, 7.36. Found: C, 92.64; H, 7.63. Picrate, calcd. for $C_{19}H_{18}\cdot C_6H_4O_7N_3$: N, 8.85. Found: N, 8.92.

9,10-Dihydro-10-methyl-1,2-benzanthracene (XI).—A solution of 0.75 g. of 10-methyl-1,2-benzanthracene in 50 cc. each of benzene and ether was stirred with a 1-g. lump of sodium under nitrogen for twenty-four hours, the solution was decolorized with alcohol, washed with dilute acid and evaporated. One crystallization from methanol gave 0.64 g. (85%) of product, m. p. 91–94°, and on further crystallization the compound formed colorless, refractive, diamond-shaped prisms, m. p. 94.4–94.9°. Under ultraviolet light the crystals, viewed edgewise, showed a faint purple-blue fluorescence. The picrate forms orange-yellow needles from methanol, m. p. 112.5–113.5°.

Anal. Calcd. for $C_{19}H_{16}$: C, 93.41; H, 6.60. Found: C, 93.32: H, 6.67. Picrate, calcd. for $C_{19}H_{16}\cdot C_6H_3O_7N_3$: N, 8.88. Found: N, 8.85.

Oxidation of 100 mg. of the hydrocarbon with 170 mg. of chromic anhydride in acetic acid gave 25 mg. of crude 1,2-benzanthraquinone and on crystallization from methanol this melted at 167–168° and gave no depression when mixed with an authentic sample.

1',2',3',4',9,10-Hexahydro-10-methyl-1,2-benzanthracene (X). (a) By Reduction with Sodium and Amyl Alcohol.—Reduced exactly as described for 1,2-benzanthracene, the 10-methyl compound (1 g.) gave a colorless oil (1 g.) with a brilliant blue fluorescence. This did not crystallize after standing for one month at 2–4° and it yielded no addition compound with picric acid. An alcoholic solution deposited solid material when chilled with Dry-Ice, but the substance liquefied on warming to 0°. The oil seemed to be susceptible to autoxidation, for unless the analysis was done promptly the percentage of carbon was low. An analysis of a fresh sample is reported below.

A solution of 100 mg. of the hydrocarbon with 160 mg. of chromic anhydride in acetic acid (heat evolved at 25°), was kept at 50–60° for two hours and refluxed for ten minutes and diluted. The crystalline product on purification from methanol gave 25 mg. (24%) of yellow needles, m. p. 155.5–156°, giving no depression when mixed with synthetic 1',2',3',4'-tetrahydro-1,2-benzanthraquinone.[8]

(b) From the 1',2',3',4'-Tetrahydride.—Conducting the addition of sodium and alcoholysis as above, 300 mg. of the tetrahydride gave 240 mg. of colorless, oily distillate. Oxidation of 129 mg. of the hydrocarbon gave 56 mg. of the tetrahydrobenzanthraquinone, m. p. 154–156°, identified by mixed melting point determination.

(c) From the 9,10-Dihydride.—The dihydro compound (0.48 g.) in 75 cc. of alcohol with 50 mg. of Adams catalyst and 0.2 cc. of ferric chloride solution (no reaction without promoter) absorbed 2 moles of hydrogen in six hours and gave 0.42 g. (88%) of colorless, distilled hydrocarbon. On oxidation, 124 mg. of the oil gave 63 mg. of the above quinone, m. p. 155–157°, identical with the synthetic material.

Analyses conducted with freshly prepared samples obtained by the three methods gave the following results.

Anal. Calcd. for $C_{19}H_{20}$: C, 91.87; H, 8.13. Found: (a) C, 91.72; H, 8.09; (b) C, 91.67; H, 8.26; (c) C, 91.85; H, 8.37.

5,6,7,8-Tetrahydro-1,2-benzanthranyl-10-acetate (XVI).—A solution of 2.5 g. of 1,2-benzanthranyl-10-acetate (XV)[9b] in 125 cc. of glacial acetic acid with 0.1 g. of Adams catalyst absorbed 2 moles of hydrogen in four hours, and some of the product had crystallized at this point. The collected product on recrystallization from benzene–ligroin melted at 158–159°; yield, 1.95 g. (77%). Further purification from benzene–ligroin and from methanol gave colorless prisms, m. p. 159–159.5°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.74; H, 6.24. Found: C, 82.65; H, 6.40.

5,6,7,8-Tetrahydro-10-acetoxy-1,2-benz-3,4-anthraquinone (XVII).—Oxidation of 1 g. of XVI in 50 cc. of glacial acetic acid with 0.91 g. of chromic anhydride at 55–60° for one and one-half hours gave, after precipitation and four crystallizations from benzene–ligroin, 0.15 g. (13%) of the quinone as reddish orange prisms, m. p. 232–233°.

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.95; H, 5.09.

The quinoxaline derivative formed short yellow needles, m. p. 276–278°, from glacial acetic acid.

Anal. Calcd. for $C_{26}H_{20}O_2N_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.58; H, 5.88; N, 7.71.

1',2',3',4',5,6,7,8-Octahydro-1,2-benzanthranyl-10-acetate (XIX). (a) From the 1',2',3',4'-Tetrahydride.—A solution of 0.95 g. of the tetrahydride in 50 cc. of glacial acetic acid using 0.1 g. of Adams catalyst absorbed 2 moles of hydrogen in three and one-half hours (hydrogenation was proceeding at this point at a slow but steady rate). The solution darkened rapidly on filtration of the catalyst and exposure to the air and some tarry material separated on concentrating the solution and adding water. This was removed with Norite, and the filtered solution deposited 0.5 g. (52%) of pink, crystalline product. m. p. 120–123°. Three crystallizations from methanol gave colorless, short needles, m. p. 129.3–129.6°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.55. Found: C, 81.58; H, 7.72.

(b) Through the 5,6,7,8-Tetrahydride.—A solution of 2 g. of 1,2-benzanthranyl-10-acetate in 100 cc. of glacial acetic acid with 0.1 g. of Adams catalyst absorbed 4 moles of hydrogen in forty-four hours. After removal of the catalyst and dilution with water, the product separated in a colloidal condition and coagulated only in three days. One crystallization from ligroin gave 1.1 g. (53%) of material melting at 118–122°; a further crystallization from this solvent and two from methanol brought the melting point to 129–129.5° (0.85 g.) and the substance did not depress the melting point of the above product (a).

Summary

Catalytic hydrogenation of 1,2-benzanthracene and of its 10-methyl and 10-acetoxy derivatives in the presence of Adams catalyst (usually with a promoter) results in the saturation of the terminal ring of the anthracene system, giving 5,6,7,8-tetrahydrides. With the acetoxy compound, which is more susceptible to attack than the other two substances, further hydrogenation results in the reduction of the other terminal ring. There is no indication that the hydrogenation of the benzanthracene derivatives proceeds through the intermediate fixation of hydrogen to the *meso*-positions, and indeed in one case a 9,10-dihydride was found to yield on hydrogenation a product quite different from the 5,6,7,8-tetrahydride obtained directly from the aromatic hydrocarbon.

On reduction with sodium and amyl alcohol, 1,2-benzanthracene and 10-methyl-1,2-benzanthracene are converted into 1′,2′,3′,4′,9,10-hexahydro derivatives.

New derivatives of the carcinogenically active 10-methyl-1,2-benzanthracene which have been submitted to biological tests include the 9,10-dihydride, the 1′,2′,3′,4′- and 5,6,7,8-tetrahydrides, and the 1′,2′,3′,4′,9,10-hexahydride.

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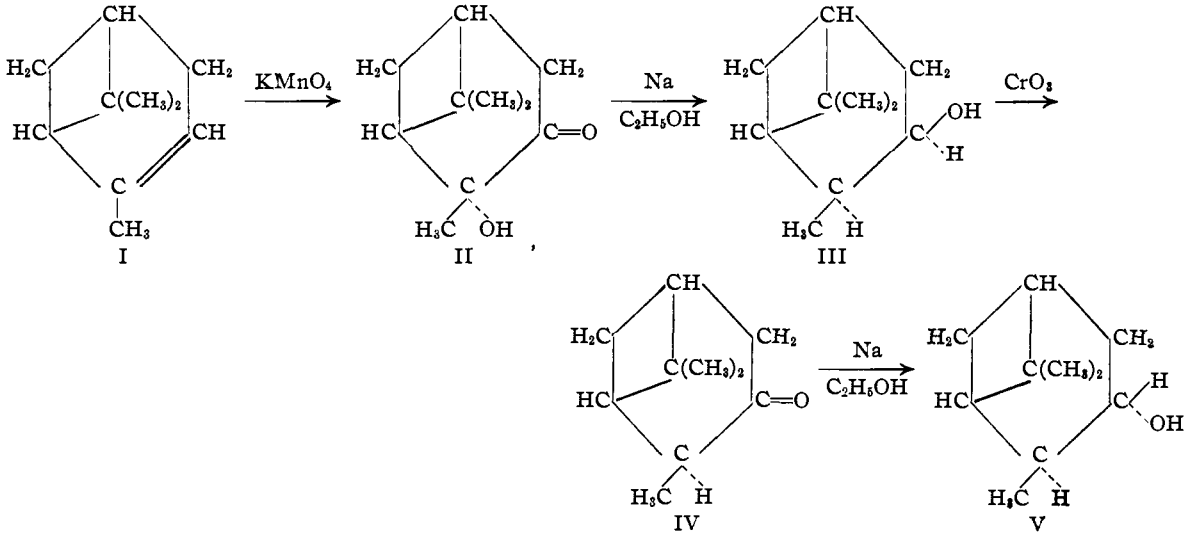
Stereochemistry of Pinocampheols

BY TSUTOMU KUWATA

As pinocampheol is an alcohol of a bicyclic terpene, the existence of four diastereoisomeric compounds may be assumed. E. Gildemeister and H. Köhler[1] obtained *l*-pinocampheol (m. p. 67–68°) by reducing *l*-pinocamphone present in hyssop oil, and O. Wallach[2] synthesized *i*-pinocampheol (liquid) from nitrosopinene. H. Schmidt and L. Schulz[3] claimed to have prepared a new pinocampheol (m. p. 57°) by reducing *l*-pinocarveol from the oil of *Eucalyptus globulus*. The configurations of the pinocampheols, however, have not been studied extensively.

The present author has found a new method of synthesis of pinocampheol from α-pinene and has been able to confirm, to some extent, the diastereoisomeric relations between these alcohols.



When one mole of *d*-α-pinene (I) is oxidized in a medium of 90% aqueous acetone with powdered potassium permanganate corresponding to the amount of two atoms of oxygen, a new ketol, levorotatory 1-hydroxypinocamphone (II), is produced. The inversion of optical sign would be

(1) E. Gildemeister and H. Köhler, *Chem. Zentr.*, **80**, II, 2158 (1909).

(2) O. Wallach, *Ann.*, **300**, 288 (1898).

(3) H. Schmidt and L. Schulz [*Schimmel Ber.*, 97 (1934)] named this pinocampheol *cis*-pinocampheol.