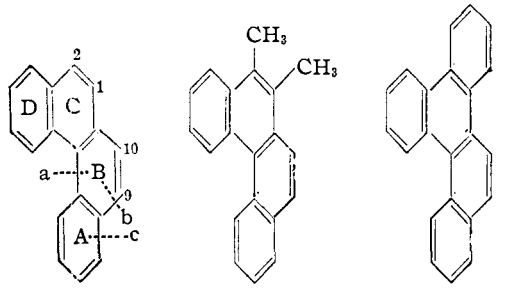
[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

1,2,3,4-Dibenzphenanthrene and Its Derivatives. III. Synthesis of 1,2-Dimethyl-3,4-benzphenanthrene[1]

BY FELIX BERGMANN AND JACOB SZMUSZKOWICZ[2]

Among the tetracyclic aromatic ring compounds, only 3,4-benzphenanthrene (I) shows feeble carcinogenic activity.[3] Introduction of a methyl group into the 1- or 2-position enhances tumor production[4] and attachment of an additional ring at the same points leads to 1,2,3,4-dibenzphenanthrene (III), a strong blastogenic agent,[5] which occupies a central position in the system relating the carcinogenic activity of hydrocarbons to their molecular structure.[6,7] On the basis of experimental material in other series, it could be predicted that 1,2-dimethyl-3,4-benzphenanthrene (II) would be nearly as strong a carcinogenic agent as dibenzphenanthrene. However, all attempted syntheses of the interesting hydrocarbon II have failed so far.



I II III

3,4-Benzphenanthrene and its 1- and 2-alkyl derivatives have been prepared by a number of different methods:

1. Cook,[8] who applied the Pschorr synthesis to α-(2-naphthyl)-β-(*o*-aminophenyl)-acrylic acid, obtained a mixture of 1,2-benzanthracene and 3,4-benzphenanthrene derivatives. A more successful modification of this process uses *o*-halogen instead of the *o*-amino group to effect ring closure.[9] In this group of syntheses, ring B is closed along line (a).

2. Hewett[10] also achieved ring closure in the same ring along line (b) starting with 1-phenyltetralin-2-acetic acid. This reaction leads to 3,4-benzphenanthrene itself and its 2-alkyl derivatives. A double ring closure at carbon atoms 2 and 9, starting with β-benzhydrylglutaric acid, was used by Newman and Joshel[11] for the preparation of the same hydrocarbons.

3. γ-(4-Phenanthryl)-butyric acid was used as starting material for the synthesis of I by Bachmann and Edgerton.[12] Here ring A is finally attached to the phenanthrene molecule by ring closure at line (c).

4. Ganguly[13] reported the successful cyclization of 2-(β-phenethyl)-tetralol-1 again along line (a) to obtain the ring skeleton of 3,4-benzphenanthrene.

All these methods suffer from difficulties in the preparation of the starting materials and from poor yields due to the great number of steps involved.

The simplest approach to compound I would undoubtedly be to start with a naphthalene derivative containing ring A, C and D and to complete ring B by introduction of carbon atoms 9 and 10. However, a negative result was reported ten years ago in the fundamental experiment, *viz.*, the condensation of α-(Δ¹-cyclohexenyl)-naphthalene (IV, $R_1 = R_2 = H$) with maleic anhydride.[14] It was then stated that a striking difference was observed between corresponding cyclopentenyl and cyclohexenyl derivatives: the former underwent condensation readily, whereas the latter remained refractive under various experimental conditions. On reinvestigation we have now found that this difference is a matter of degree. Thus α-(Δ¹-cyclopentenyl)-naphthalene reacts with maleic anhydride in boiling xylene,[15] whereas the corresponding cyclohexenyl derivative requires a temperature of 220–230°. Even then, however, we did not succeed in isolating the pure adduct (V, $R_1 = R_2 = H$), but by dehydrogenation of the crude, amorphous adduct obtained the desired 3,4-benzphenanthrene-9,10-dicarboxylic anhydride (VI, $R_1 = R_2 = H$).[16] Decarboxylation then yielded I. The method as developed makes it possible to prepare substantial amounts of various members of the 3,4-benzphenanthrene series in a reasonably short time. Application of the procedure to 1-methyl-4-(Δ¹-cyclohexenyl)-naphthalene (IV, $R_1 = CH_3$; $R_2 = H$) yielded 2-methyl-3,4-benzphenanthrene; in an analogous

(1) Part I, F. Bergmann and Eschinazi, THIS JOURNAL, **65**, 1413 (1943); Part II, *ibid.*, **66**, 183 (1944).

(2) Part of a thesis submitted to the Hebrew University, Jerusalem, 1947.

(3) Barry, *et al.*, *Proc. Roy. Soc.* (*London*), **B117**, 318 (1935).

(4) Bachmann, *et al.*, *ibid.*, **B123**, 343 (1937).

(5) Badger, *et al.*, *ibid.*, **B129**, 439 (1940).

(6) Hewett, *J. Chem. Soc.*, 293 (1940).

(7) F. Bergmann, *Cancer Research*, **2**, 660 (1942).

(8) Cook, *J. Chem. Soc.*, 2524 (1931).

(9) Hewett, *ibid.*, 1286 (1938); I. G. Farbenindustrie, British Patent 459,108.

(10) Hewett, *ibid.*, 596 (1936).

(11) Newman and Joshel, THIS JOURNAL, **60**, 485 (1938); **62**, 972 (1940).

(12) Bachmann and Edgerton, *ibid.*, **62**, 2970 (1940).

(13) Ganguly, *C. A.*, **36**, 3172 (1942).

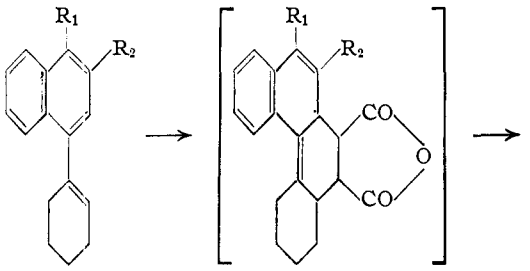
(14) E. Bergmann and F. Bergmann, THIS JOURNAL, **59**, 1443 (1937).

(15) Bachmann and Kloetzel, *ibid.*, **60**, 2204 (1938).

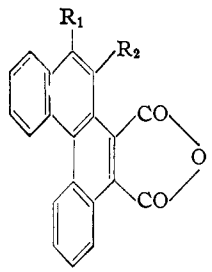
(16) Although this substance could be designated as the 1,2-dicarboxylic anhydride, we prefer the alternative numbering which is in line with the numbering of the methyl derivatives described below.

way, 1,2-dimethyl-4-(Δ^1-cyclohexenyl)-naphthalene (VI, $R_1 = R_2 = CH_3$) led to the desired new hydrocarbon (II).[17]

A similar difference in reactivity was observed with 9-(Δ^1-cyclopentenyl)-phenanthrene and the corresponding cyclohexenyl derivative (VII). The former gave a nearly quantitative yield of crystalline adduct when heated to 80–90° with ten moles of maleic anhydride. Compound VII, on the other hand, upon condensation at 220–230° gave an amorphous adduct which was dehydrogenated to the anhydride VIII. Decarboxylation of VIII led to 1,2,3,4-dibenzphenanthrene (III).



IV V



VI

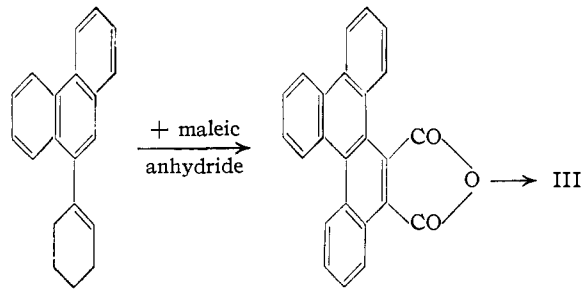
The 4-bromo-1-methylnaphthalene required for the preparation of the cyclohexenyl derivative (IV, $R_1 = CH_3$; $R_2 = H$) was synthesized according to the directions of Fieser and Bowen[18] *via* the corresponding 4-sulfonic acid. An analogous procedure for 4-bromo-1,2-dimethylnaphthalene, the starting material for (IV, $R_1 = R_2 = CH_3$) was not suitable because sulfonation of 1,2-dimethylnaphthalene produces a mixture of sulfonic acids among which are found only 30% of the required isomer.[19] Both methyl groups exert their directing influence simultaneously, the α-methyl group favoring substitution at position 4, the β-methyl group at position 6.[20] Therefore we followed the procedure of Hewett[6] for the direct bromination of 1,2-dimethylnaphthalene. A mixture is obtained, and it is necessary to select the appropriate fraction as judged by the melting point of the picrate; in this way it was possible to isolate 38% of the required 4-bromo derivative.

(17) This new compound is at present under biological test at the Cancer Laboratories of the Hebrew University, Jerusalem.

(18) Fieser and Bowen, THIS JOURNAL, **62**, 2103 (1940).

(19) Kruber and Schade, *Ber.*, **68**, 11 (1935).

(20) Dziewonski, Schoenowna and Waldmann, *ibid.*, **58**, 1211 (1925).



VII VIII

Experimental Part[21]

Preparation of Cyclohexenylnaphthalenes (IV)

1. **α-(Δ^1-Cyclohexenyl)-naphthalene** (IV, $R_1 = R_2 =$ H) was prepared in 75% yield according to Weiss and Woidich[22]; b. p. 125° (0.08 mm.).

2. **1-Methyl-4-(Δ^1-cyclohexenyl)-naphthalene** (IV, $R_1 = CH_3$; $R_2 =$ H) was obtained by the Grignard reaction of 1-methyl-4-bromonaphthalene. This compound reacted with magnesium only in the presence of an entrainer: a mixture of 1-methyl-4-bromonaphthalene (44 g., 0.2 mole) and methyl iodide (28.5 g., 0.2 mole) in ether–benzene (1:1, 200 cc.) was added slowly to magnesium turnings (10 g.). After the Grignard compound had been formed, the solution was cooled to 0°, and cyclohexanone (40 g., 0.4 mole) in benzene (100 cc.) was added. The mixture was refluxed for three hours and then worked up as usual. Dehydration of the crude carbinol was effected by heating to 160° in the presence of sodium bisulfate. The hydrocarbon (IV, $R_1 = CH_3$, $R_2 =$ H) was obtained in 50% yield as a light-brown sirup, b. p. 127° (0.04 mm.). An analytically pure sample was prepared by conversion of the hydrocarbon to the picrate in ethanol solution; decomposition of the picrate yielded a nearly colorless oil, b. p. 118–120° (0.04 mm.), $n^{29}D$ 1.6064.

Anal. Calcd. for $C_{17}H_{18}$: C, 91.9; H, 8.1. Found: C, 92.0; H, 8.0.

The picrate crystallized from butanol in long thin, intense yellow rods, m. p. 156–157°.

Anal. Calcd. for $C_{23}H_{21}O_7N_3$: C, 61.2; H, 4.7; N, 9.3. Found: C, 61.2; H, 5.0; N, 9.1.

3. **1,2-Dimethyl-4-(Δ^1-cyclohexenyl)-naphthalene** (IV, $R_1 = R_2 = CH_3$).—1,2-Dimethylnaphthalene (213 g.) in carbon tetrachloride (600 cc.) was brominated at room temperature by adding a solution of bromine (70 cc.) in carbon tetrachloride (250 cc.) during one and three-quarter hours. Stirring was continued for two and one-half hours and then half of the solvent distilled off. The remainder was washed with water and soda solution and fractionated. The fractions boiling between 120–160° (0.2 mm.) gave a picrate, m. p. 107°,[23] and were selected for further rectification. The pure bromo derivative boils at 125–130° (0.2 mm.); yield 123 g. (38%). Head and tail fractions gave higher-melting picrates and were therefore discarded.

The Grignard reaction of 1,2-dimethyl-4-bromonaphthalene with cyclohexanone was carried out exactly as described under 2. The crude dehydration product was distilled *in vacuo*, b. p. 140° (0.2 mm.) and solidified upon trituration with methanol. It crystallized from ethanol in rods, m. p. 79–79.5°; yield, 64%.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.5; H, 8.5. Found: C, 91.7; H, 8.6.

The **picrate** crystallized from ethanol in slender, orange needles, m. p. 119–120°.

Anal. Calcd. for $C_{24}H_{23}O_7N_3$: C, 61.9; H, 4.9. Found: C, 61.6; H, 4.9.

(21) The melting points are uncorrected.

(22) Weiss and Woidich, *Monatsh.*, **46**, 453 (1925).

(23) Hewett (see footnote 6) reports the m. p. 108–109°.

TABLE I

3,4-BENZPHENANTHRENE-9,10-DICARBOXYLIC ANHYDRIDE AND DERIVATIVES (VI AND VIII)

	Compounds	M. p., °C.	Solvent for crystn.	Crystal form	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
1	VI, $R_1 = R_2 = H$	249–250	Butyl acetate	Yellow needles	$C_{20}H_{10}O_3$	80.5	3.4	80.45	3.4
2	VI, $R_1 = CH_3$, $R_2 = H$	264–265	Acetic anhydride	Long yellow needles	$C_{21}H_{12}O_3$	80.8	3.8	80.6	4.0
3	VI, $R_1 = R_2 = CH_3$	260–261	Acetic anhydride	Brown needles	$C_{22}H_{14}O_3$	81.0	4.3	81.3	4.0
4	VIII	292–293	Acetic anhydride–acetic acid	Yellow elongated rods	$C_{24}H_{12}O_3$	82.8	3.4	82.7	3.7

TABLE II

3,4-BENZPHENANTHRENE AND DERIVATIVES

	Compound	M. p., °C.	Solvent for recrystallization	Crystal form	Picrate M. p., °C.	Picrate Solvent for recrystallization	Picrate Crystal form
1	3,4-Benzphenanthrene	68[a]	Ethanol	Long rods	125–126	Ethanol	Red, branched needles
2	2-Methyl-3,4-benzphenanthrene	71[b]	Ethanol	Leaflets	132–133	Ethanol	Brick-red needles
3	1,2-Dimethyl-3,4-benzphenanthrene	99–100[c]	Ethanol	Rectangular blocks	123–124[d]	Ethanol	Dark-red rods
4	1,2,3,4-Dibenzphenanthrene	114–115[e]	Acetic acid	Clusters of needles	140	Acetic acid	Red needles

[a] Cook, *J. Chem. Soc.*, 2524 (1931), reports m. p. 68 and 126–127°, respectively. [b] Hewett, *ibid.*, 596 (1936), gives m. p. 70 and 133.5°, respectively. [c] *Anal.* Calcd. for $C_{20}H_{16}$: C, 93.75; H, 6.25. Found: C, 93.6; H, 6.4. [d] *Anal.* Calcd. for $C_{26}H_{19}O_7N_3$: C, 64.3; H, 3.9; N, 8.7. Found: C, 64.5; H, 3.9; N, 8.9. [e] Hewett, *J. Chem. Soc.*, 193 (1938), reports the melting points 115 and 140°, respectively; *cf.* also Bradsher and Rapoport, THIS JOURNAL, 65, 1646 (1943).

4. **9-(Δ¹-Cyclohexenyl)-phenanthrene** was prepared in 85% yield by dehydrating 1-(9-phenanthryl)-cyclohexanol-1 thermally at 160°. This considerable improvement over the 20% yield reported by Bergmann and Bergmann,[14] was achieved by avoiding acid catalysts during the dehydration of the carbinol.

Condensation with Maleic Anhydride

A mixture of the appropriate cyclohexenyl derivative (0.1 mole) and maleic anhydride (50 g.) was heated for four hours to 220–230°. The black mass was then dissolved in hot acetic acid and water was slowly added. The amorphous yellowish precipitate obtained by this procedure could not be crystallized. It was therefore dried by a stream of air and directly dehydrogenated. If necessary, it was purified before dehydrogenation by dissolving in sodium hydroxide and reprecipitation by means of hydrochloric acid.

1. The adduct of α-(Δ¹-cyclohexenyl)-naphthalene (3 g.) was heated with sulfur (1.3 g., 4 atoms). A vigorous reaction started at about 260°. The mixture was kept for twenty-five minutes at 260–280° and was then distilled in a tube between 250–290° (0.1 mm.). The brown oil that distilled solidified immediately; yield 40%. The crude product, m. p. 185–190°, was resublimed in a high vacuum and could then be recrystallized from butyl acetate (see Table I).

This tedious procedure is unsuitable for working up larger quantities. It was observed, however, that material of sufficient purity for the next step could be secured by extracting the crude dehydrogenation product with butyl acetate and precipitating with petroleum ether.

2. The adduct of 1-methyl-4-(Δ¹-cyclohexenyl)-naphthalene was dehydrogenated as above and distilled in a tube at 230–300° (0.1 mm.). The resulting brown oil solidified immediately. The crude product upon recrystallization from acetic acid melted at 235–237°; yield 38%. It was necessary to resublime the anhydride (VI; $R_1 = CH_3$; $R_2 = H$), in order to obtain an analytically pure sample (see Table I).

3. The adduct of 1,2-dimethyl-4-(Δ¹-cyclohexenyl)-naphthalene was treated as described under 2. The crude anhydride (VI, $R_1 = R_2 = CH_3$), upon crystallization from acetic acid melted at 235–238°; yield, 36%. After resublimation, the m. p. could again be raised by about 25° (see Table I).

4. The adduct of 9-(Δ¹-cyclohexenyl)-phenanthrene was dehydrogenated at 270–290° for fifteen minutes and then at 320–340° for half an hour. The aromatized product was distilled in a tube between 270–300° (0.1 mm.).[24] The brown sirup solidified immediately, m. p. 240°. After resublimation, the product could be obtained in an analytically pure condition (see Table I).

Decarboxylation

General Procedure.—The aromatic anhydride (5 g.), suspended in dioxane (30–50 cc.), was added to a hot solution of barium hydroxide (25 g.). The precipitate was dried at 70° and then ground thoroughly with addition of barium hydroxide (10 g.) and copper bronze (7 g.). Decarboxylation was carried out in all cases at about 320°[25] and it was observed that application of a water-pump vacuum during the reaction increased the yield considerably. The yellow oils so obtained represented about 40% of the theoretical yield. They were converted directly into the picrates, and the latter recrystallized if necessary. By decomposition of the picrates, the free hydrocarbons were isolated and purified by distillation and recrystallization.

Acknowledgement.—The authors wish to express their thanks to Prof. L. F. Fieser for his help and criticism in the preparation of this manuscript.

Summary

In contrast to previous findings, α-(Δ¹-cyclohexenyl)-naphthalene and its methyl homologs and 9-(Δ¹-cyclohexenyl)-phenanthrene react with maleic anhydride if drastic conditions are applied. This reaction provides a convenient route to 3,4-

(24) If the dehydrogenation was carried out below 300°, the substance contained a certain amount of hydroaromatic anhydrides, and therefore its decarboxylation product could not be obtained in crystalline form.

(25) In the case of dibenzphenanthrene-9,10-dicarboxylic anhydride (X) a somewhat higher temperature (~340°) was required.

benzphenanthrene and its derivatives, and to 1,2,3,4-dibenzphenanthrene.

1,2-Dimethyl-3,4-benzphenanthrene, a new compound of interest as a potential carcinogenic agent, has been prepared in this way.

REHOVOTH, PALESTINE RECEIVED JANUARY 31, 1947

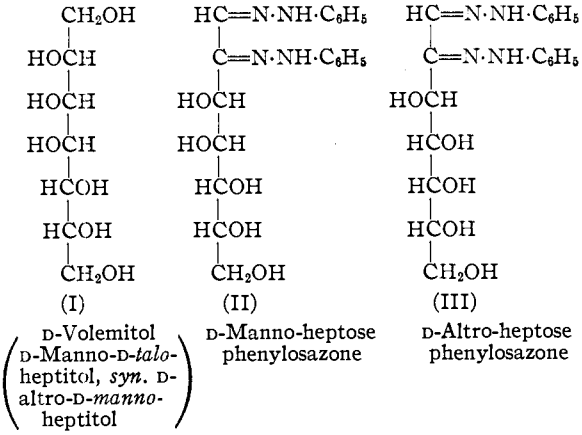
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Identification of Emil Fischer's "Phenyl-volemosazone" as D-Mannoheptose Phenylosazone

BY W. T. HASKINS AND C. S. HUDSON

In a recent review[1] one of us pointed out that it was not possible to decide from available data the configuration of the phenylosazone (melting at 196° with decomposition) which Emil Fischer[2] obtained from the products of the oxidation of the naturally occurring volemitol by sodium hypobromite. He named the substance "phenyl-volemosazone" and proved by its analysis that it belongs in the heptose series, and that accordingly volemitol is a heptitol. A decision concerning the last question was the object of this investigation.

The configuration of volemitol is now known (I) and it has become evident in consequence that if "phenyl-volemosazone" is a normal osazone, as is highly probable, its configuration is limited to that of D-mannoheptose phenylosazone (II) or D-altroheptose phenylosazone (III). The formulas II and III are written in the usual form that shows solely the fundamental configuration, devoid of indications of rings that may possibly be present.



Recently we have had occasion to prepare considerable quantities of the phenylosazones II and III in the course of a study of the preparation of phenylosotriazoles from them,[3] and it has become evident that, while the melting points of these phenylosazones are too nearly alike for purposes of identification, their rotations clearly lead to a distinction. With the monomethyl ether of ethylene glycol (methyl Cellosolve) as solvent, one of them (III) is strongly levorotatory and exhibits no mutarotation, whereas the other (II) is strongly dextrorotatory with a large, though slow, mutarotation to an end value that is still a dextrorotation (see Table I). These data have now been applied for the purpose of establishing the configuration of Fischer's "phenyl-volemosazone." We followed precisely the detailed directions of Fischer for oxidizing volemitol with sodium hypobromite, for obtaining a phenylosazone from the oxidation products, and for recrystallizing the crude phenylosazone. From 10 g. of pure volemitol (m. p. 153°) there was obtained 1.5 g. of crude phenylosazone, which is near the yield that he reported. Our substance proves to be D-mannoheptose phenylosazone (see Table I). Although an assumption that some D-altroheptose phenylosazone was produced during the reactions is hardly avoidable, we did not detect any of this substance in the crude phenylosazone that crystallized from the complex reaction mixture, and one recrystallization sufficed to bring the substance to full purity. These facts lead us to believe that the same phenylosazone crystallized in Fischer's experiment and that his "phenyl-volemosazone" was D-mannoheptose phenylosazone. The customary measurements of melting points are recorded in the table but it should be remembered that these osazones decompose on melting; the mixed melting points fairly confirm the identification but the rotation measurements are the real basis for it. The amount of our material did not suffice for the preparation of a phenylosotrizole in the volemitol series but this appears unnecessary in view of the definitive data from the rotations.

The name "volemose," which carries the final syllable that is customary in the names of sugars, was originally suggested by Fischer in a cursory way as the name of the "sugar" which gave rise to the "phenyl-volemosazone." Such chemical oxidations of polyhydric alcohols yield in general a complex mixture of reducing substances and it is evident that "phenyl-volemosazone" could have arisen from the aldose D-manno-D-*talo*-heptose, the ketose D-manno-heptulose, or from D-manno-heptosone resulting from their further oxidation. It could not have arisen from D-manno-D-*gala*-heptose in such experiments because the configura-

(1) Hudson, in "Advances in Carbohydrate Chemistry," Vol. I, Academic Press Inc., New York, 1945, p. 32.

(2) Fischer, *Ber.*, **28**, 1973 (1895).

(3) Haskins, Hann and Hudson, THIS JOURNAL, **69**, 1050 (1947).