THE PARTIAL SYNTHESIS OF 1',9-DIMETHYL-1,2-BENZANTHRACENE

DISSERTATION

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By

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INTRODUCTION

The synthesis and study of polynuclear hydrocarbons capable of producing cancer in experimental animals have been under investigation for many years. Since any knowledge of the manner in which cancer originates in human beings may pave the way toward possible methods of control, therapy, and ultimate cure, the polynuclear hydrocarbons with carcinogenic properties have become of prime importance. Through their use a means is furnished for inducing cancerous growths under relatively controlled conditions, thus affording some insight into the mechanism of tumor induction.

In the present investigation we were interested in the synthesis of 1',9-dimethyl-1,2-benzanthracene, a hydrocarbon which theoretically should exhibit high carcinogenic potency. We were aware, from the outset, of some of the difficulties involved in approaching the synthesis of this "sterically impossible" compound. A partial synthesis of 1',9-dimethyl-1,2-benzanthracene has been accomplished, and several steps toward the total synthesis have been explored.
HISTORICAL

It has been known for a number of years that certain coal tars and mineral oils are capable of producing cancer. The first observation of this phenomenon was made by Yamagiwa and Ichikawa\(^1\), who noted the carcinogenic activity of some of the distillation products of coal tar. Experiments by Bloch and Dreifuss\(^2\) led them to conclude that the carcinogenically active component was a high-boiling neutral compound which formed a stable picrate. Support for this conclusion was soon provided by Kennaway\(^3\), who was able to produce carcinogenic tars by the pyrolysis of acetylene or isoprene in an atmosphere of hydrogen. It should be noted, however, that although these experiments indicate that the active compounds are hydrocarbons, it does not necessarily follow that all high-boiling hydrocarbons from coal tar are carcinogenic. As a matter of fact, most of them are not.

In 1950, Hieger\(^4\) found that tars and mineral oils which induce cancer of the skin, either as the

1-Yamagiwa and Ichikawa, Mitteil. med. Fakultat, Kaiser Wilhelm Univ., Tokyo, \textbf{15}, 295 (1915)
2-Bloch and Dreifuss, Schweiz. med. Wochenschr., \textbf{2}, 1033 (1921)
4-Hieger, Biochem. J., \textbf{24}, 505 (1930)
result of industrial disease or of animal experiments, possessed specific fluorescence spectra with bands at 4000 Å, 4180 Å, and 4400 Å. The pure fractions from pitch gave the same characteristic spectra with bands at 4000 Å, 4180 Å, and 4400 Å and were in every case carcinogenic. This gave, then, a close correlation between spectrographic and biological tests.

The first compound of known structure discovered to possess carcinogenic activity was 1,2,5,6-dibenzanthracene\(^1\) (I). Soon after this discovery, 3,4-benzpyrene (II) was isolated from pitch and shown to be carcinogenic\(^2\). The following year Cook and Haslewood\(^3\) reported that

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\end{align*}
\]

methylcholanthrene (III), obtained by the degradation of the bile acids, was a potent carcinogen. Most of the

---

1-Kennaway and Hieger, Brit. Med. J., 1, 1044 (1930)  
3-Cook and Haslewood, ibid., 428, (1934)
hydrocarbons which are known to produce cancer contain the 1,2-benzanthracene nucleus, and it can be seen that the compounds above may be considered as derivatives of 1,2-benzanthracene (IV). On the other hand, the parent hydrocarbon itself, 1,2-benzanthracene, exhibits no carcinogenic activity¹.

Out of these investigations there arose an entirely new field of endeavor in organic chemistry: the synthesis of polycyclic aromatic hydrocarbons related to 1,2-benzanthracene. There are twelve points of monosubstitution in the 1,2-benzanthracene molecule, and since the molecule is possessed of latent carcinogenic activity, a systematic study of mono- and dialkyl derivatives was instituted in England by Cook and his co-workers and, in this country, by Fieser and his co-workers. Cook², along

2-Cook et al., ibid., 1087 (1930); 456 (1932); 1592(1933)
with Fieser and Newman, found that the 5- and 10- positions in 1,2-benzanthracene were especially effective structurally in enhancing carcinogenic activity.

The desirability of preparing 1',9-dimethyl-1,2-benzanthracene (V) originated from its theoretical relationship to 3,4-benzpyrene (II). Fieser regarded 3,4-benzpyrene as a 1',9-disubstitution product of 1,2-benzanthracene, derivable from (V) by ring closure through the methyl groups. After first assuming a corresponding bond structure in the 1,2-benzanthracene part of the molecule, it was postulated that the simplified structure would resemble 3,4-benzpyrene and might show similar carcinogenic potency.

If (V) is considered as a derivative of phenanthrene (VI), it can be named 4.5-dimethyl-2,3-benzphenanthrene. The structural feature that makes the synthesis

3-Fieser and Lothrop, ibid., 58, 749 (1936)
of (V) of peculiar interest is the 4,5-dimethylphenanthrene grouping. Early attempts to synthesize 4,5-dimethylphenanthrene itself have been unsuccessful\(^1,2\), and the possibility of the existence of this type of compound was doubted on steric grounds\(^3\). Newman's synthesis of 4,5-dimethylchrysene (VII)\(^4\), the syntheses of 4,5,8-trimethyl-1-phenanthryl acetic acid (VIII)\(^5\), 1-methylbenzo[c]-phenanthrene (IX)\(^6\), and the recently reported syntheses of 4,5-dimethylphenanthrene (X)\(^7\) and 1,12-dimethylbenzo[c]-phenanthrene (XI)\(^8\) indicate that compounds of the 4,5-dimethylphenanthrene type are indeed capable of existence and can be synthesized. The compound, 4,5-dimethylchrysene (VII), bears the same relationship to 3,4-benzpyrene (II) that 1,9-dimethyl-1,2-benzanthracene does, but with

\[
\text{VII} \\
\text{VIII}
\]

3-Cook and Kennaway, Am. J. Can., 32, 53 (1937)
5-Newman and Hussey, ibid., 69, 3023 (1947)
6-Newman and Whitehouse, ibid., 71, 3664 (1949)
7-Newman and Wheatley, ibid., 70, 1913 (1948)
8-Wolf, M., Ph.D. Dissertation, The Ohio State University, 1951
this significant difference: that (VII) does not possess the 1,2-benzanthracene nucleus.

The difficulty expected in the synthesis of compounds like (V) is associated with the belief that there is steric hindrance between the methyl groups, and calculations show that the volume of the methyl groups is great enough to cause such interference. It was consid-

\[
\text{ IX } \quad \begin{array}{c}
\text{H}^+ \\ \text{CH}_3 \\
\end{array} \\
\text{ XI }
\]

\[
\text{ X } \quad \begin{array}{c}
\text{H}_2^+ \\
\text{CH}_3 \\
\end{array} \\
\text{CH}_3
\]

\[
\text{ H}^+ \\
\text{CH}_3
\]

1-Newman, op. cit.
2-Newman and Hussey, op. cit.
acid (VIII). This type of isomerism differs from that found in the biphenyl series (where the rings are not in the same plane) and has been called "isomerism of the 4,5-dimethylphenanthrene type".

The success of the synthesis of 4,5-dimethylchrysene (VII) was attributed to two factors: the introduction of the methyl groups early, when no interference was expected; and final ring closure involving a portion of the molecule far removed from, and not affected by, the interfering groups. This technique was that attempted in the proposed synthesis of 1',9-dimethyl-1,2-benzanthracene.
PREVIOUS ATTEMPTED SYNTHESSES OF 1',9-DIMETHYL-1,2-BENZANTHRACENE

All reported efforts to synthesize 1',9-dimethyl-1,2-benzanthracene failed either when attempts were made to introduce the second methyl group into the structure or when final ring closure was undertaken. Steric conditions may be presumed to have been the cause of such failure.

In the first attempt\(^1\), the anthrol (XII) was liberated from 1'-methyl-1,2-benzanthryl-9-acetate with n-butyldimagnesium bromide. This is not as readily ketonized as the anthrol from 1,2-benzanthryl-10-acetate\(^2\), which is slowly but incompletely isomerized in boiling toluene. When (XII) was refluxed for some time in toluene, part of the material was converted to a sparingly soluble condensation product, and no addition product could be obtained by treatment of the filtrate with methylmagnesium bromide.

2-Fieser and Hershberg, ibid., 59, 1030 (1937)
A second approach utilized the method of Fieser and Newman\textsuperscript{1} for the introduction of alkyl groups into either of the meso positions of 1,2-benzanthracene. The compound (XIII) was synthesized as shown below, but all attempts to add methylmagnesium bromide to the carbonyl group of the free acid or ester failed. In every case an unsaponifiable oil was obtained. The methyl group in the peri position apparently interferes with the reaction. The same workers have reported the condensation of o-chloroacetophenone with the Grignard reagent of 1-methyl-8-bromonaphthalene which gave (XIV) after dehydration. Hydrogenation proceeded very slowly, and attempts to convert the saturated product into a nitrile, amide, or acid were without success. However, Cason and Wordie\textsuperscript{2} undertook an investigation of the problem, and by the sequence here shown were able to prepare (XV).

\textsuperscript{1}Fieser and Newman, J. Am. Chem. Soc., 58, 237 (1936)
\textsuperscript{2}Cason and Wordie, J. Org. Chem., 15, 617 (1950)
In another attempt the ketone (XVI) was prepared as indicated. When treated with methylmagnesium chloride, the oil obtained after dehydration boiled over a twenty-degree range and contained a higher carbon and hydrogen percentage by analysis than expected. Hydrogen was taken up by the material without the evolution of hydrogen chloride. Fieser and Seligman, op. cit.
ide, but the product gave no crystalline picrate and contained less than one-fourth the calculated amount of chlorine.

In these laboratories effort was made to utilize the Stobbe condensation on the ketone (XVII) and diethylsuccinate. Thus, theoretically, in one step the requisite carbon atoms for the 1,2-benzanthracene nucleus could be added. In every attempt, the condensation failed. Application of the Reformatsky reaction on the same ketone was effective in one instance, but was not successfully repeated.

1-Linsk, Jacob, Ph.D. Dissertation, The Ohio State University, 1948
XVII
Figure 1

\[ \text{IIa, IIb} \]

\[ \text{IIIa, IIIb} \]

\[ \text{IVa, IVb} \]

\[ \text{Va, Vb} \]
DISCUSSION OF RESULTS

The condensation of o-tolylacetonitrile and α-bromo-ethylbenzene in the presence of sodium amide to give (I) was effected in 69-72% yield at a temperature of -78°. In one experiment the yield was as high as 89%. Acid hydrolysis of the nitrile to the acid (II) was realized in yields of 97%. Recrystallization of the acid from hydrolysis of the nitrile gave the higher melting racemate (m.p. 171.8-172.8°), but despite several recrystallizations, the lower melting racemate could not be obtained in a pure state.

Homologation of the mixture of racemates of the acid (II) via the Arnêt-Eistert reaction¹ proceeded smoothly to give 76% of homo acid (IIIa) (IIIb). The acid chloride of (II) was prepared using purified thionyl chloride², converted to the diazoketone, and this yellow diazoketone oil was rearranged with a few milliliters of a saturated solution of silver benzoate in triethylamine³. The two possible racemates of the homo acid could be isolated by manual separation after crystallization. Cyclization of the acid chloride, prepared from either racemate of the

²-Fieser, Experiments in Organic Chemistry, p.381
³-Newman and Beal, J. Am. Chem. Soc., 72, 5163 (1950)
homo acid and phosphorus pentachloride in the usual manner, proceeded with facility at 0° in the presence of anhydrous stannic chloride to give 3-o-tolyl-4-methyl-1-tetralone, (IVa)(IVb), in practically quantitative yield. Here, again, the racemates could be separated in a pure state. It is of interest to note that the high-melting racemate of the homo acid gave low-melting cyclic ketone, and the low-melting acid gave high-melting ketone. Reaction of the cyclic ketone with methyl oxalate\(^1\) afforded the glyoxalate (Va)(Vb) in almost quantitative yield.

By means of sodium amalgam\(^2\) in one instance and of sodium borohydride\(^3\) in another, attempts were made to reduce the glyoxalate to the \(\alpha\)-hydroxy lactone, which should be hydrolyzed with concentrated hydrochloric acid to the keto acid (VII).

\[ \text{1-Bachmann, Cole, and Wilds, J. Am. Chem. Soc., 62, 824 (1940)} \]
\[ \text{2-Erlenmeyer, Ber., 35, 2767 (1902)} \]
\[ \text{3-Chaikin and Brown, J. Am. Chem. Soc., 71, 122 (1949)} \]
Such a procedure is analogous to the reduction sequence used in the work of Erlenmeyer:\(^1\)

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C}_2\text{H}_5\text{CO}_2\text{CH}_3 & \xrightarrow{\text{Na} \cdot \text{H}_2\text{O}} \text{C}_6\text{H}_5\text{CHCH}_2\text{CHC}_2\text{H}_3 \xrightarrow{\text{HCl}} \\
\text{C}_6\text{H}_5\text{CHCH}_2\text{CHC}_2\text{H}_3 & \xrightarrow{\text{HCl}} \text{C}_6\text{H}_5\text{CHCH}_2\text{CHC}_2\text{H}_3\text{CO}_2\text{H}
\end{align*}
\]

Reduction by these methods and subsequent hydrolysis principally gave the cyclic ketone (IVb), but the keto acid (VIIb) could be obtained in small amounts only.

An alternate route to the keto acid was then essayed. The glyoxalate was decarboxylated\(^2\) by heating at \(180^\circ\) with pulverized Cargille boiling chips\(^*\) to give the keto ester (VI). Alkylation of (VI) with sodium methoxide\(^3\), followed by hydrolysis of the alkylation product, likewise gave almost exclusively the cyclic ketone (IVb). However, with potassium t-butoxide as the base, a 61\% yield of the keto acid was realized. In most of these alkylation experiments non-crystallizable oils were the chief product. The acid chloride

\(^1\)Erlenmeyer, op. cit.
\(^3\)From Cargille Scientific, Inc., New York, N.Y.
\(^3\)Bachmann and Johnson, J. Am. Chem. Soc., 71, 3464 (1949)
of (VIIb) could be cyclized with anhydrous stannic chloride to give one of the four theoretically possible racemates of the diketone (VIII), m.p. 178.6-179.6°, in 53% yield.

A possible difficulty in the cyclization to the desired diketone lies in the fact that when there are stereoisomers, only one seems capable of cyclization. This was the case when attempts\(^1\) to \(\text{I}^2\) were made to cyclize 1-methyl-2-phenyl-cyclopentyl-1-acetic acid:

\[
\text{\includegraphics{diagram1.png}}
\]

and 1-methyl-2[7-methoxy-\(\beta\)-naphthyl]-1-acetic acid:

\[
\text{\includegraphics{diagram2.png}}
\]

The study of scale models of these compounds indicated that that racemate leading to a trans ring fusion between the 5- and 6-membered rings was unlikely to form because of steric factors.

1-Grotta, H., Ph.D. Dissertation, The Ohio State Univ., 1949
2-Newman and Nevenzel, unpublished results
Another route by which the glyoxalate might be converted into (X) was studied. The mercaptole was desulfurated with Raney nickel to the lactone. The resulting oil was subjected to a Clemmensen reduction to give 74\% of an acidic oil (X). This approach was abandoned because of difficulties involved in purification.

At this point the present research was brought to a close due to lack of sufficient materials for further synthetic investigation.

2-Fieser and Kilmer, ibid., 61, 864 (1939)
EXPERIMENTAL\(^1,2\)

Preparation of \(\alpha\)-Bromoethylbenzene\(^3\). A solution of 145 g. (1.38 moles) of styrene in 600 ml of a chilled 30% solution of hydrogen bromide in glacial acetic acid was allowed to stand overnight in the ice chest. After pouring into ice water, a heavy oil separated. The water was removed by decantation, and the oil washed with saturated sodium chloride solution. It was then taken up in benzene and dried with anhydrous sodium sulfate. The solvent was removed, and the oil distilled to give 202 g. (78%) of pale yellow \(\alpha\)-bromoethylbenzene, b.p. 93-95\(^\circ\)/13mm.

\(\alpha\)-o-Tolyl-\(\varphi\)-phenylbutyronitrile (I). In the best of several runs, under dry nitrogen, a solution of 131 g. (1 mole) of o-tolylacetonitrile\(^4\) in 200 ml of dry toluene was rapidly added to a stirred suspension of 48 g. (1.23 moles) of sodium amide in 200 ml of dry toluene. The solution darkened, ammonia was evolved, and it was refluxed for one hour. After cooling to room temperature, 200 ml of anhydrous ether was added and the solution immersed in a dry ice-alcohol bath. With rapid stirring 200 g. (1.08 moles) of \(\alpha\)-bromoethylbenzene was added and stir-

1-Analyses marked (a) by Mrs. Edith Klotz, O.S.U., (b) by Jack Kraus, O.S.U., (c) by Clark Microanalytical Laboratory, Urbana, Illinois.
2-Final melting points reported to 0.1\(^\circ\) were observed in a Hershberg apparatus with an Anschütz thermometer.
3-Ashworth and Burkhardt, J. Chem. Soc., 1794 (1928)
ring was continued for one hour after the addition was complete. The bath was then removed and the reaction mixture allowed to come to room temperature. After refluxing for one hour the cooled solution was acidified with dilute hydrochloric acid. The organic layer was separated and washed, first with water, then with saturated salt solution, and dried with anhydrous sodium sulfate. After removal of the solvent, distillation gave 209.1 g. (89%) of colorless liquid, b.p. 151-166°/0.8 mm. After purification there was obtained 189.4 g. (80%) of \( \alpha \)-o-tolyl-\( \beta \)-phenylbutyronitrile, b.p. 168°/1.5-2.0 mm.

Analysis (a) Calcd. for \( \text{C}_{17}\text{H}_{17}\text{N} \): C, 86.8 H, 7.3

Found: C, 86.5 H, 7.2
C, 86.6 H, 6.8

\( \alpha \)-o-Tolyl-\( \beta \)-phenyl butyric acid (IIa)(IIb). A solution of 164 g. (0.7) mole of the nitrile (I) in 570 ml of glacial acetic acid, and 85 ml of water was refluxed for 72 hours. During the last hour 100 ml of water was added and most of the acetic acid removed under diminished pressure by means of the water pump. The cooled residue was extracted with benzene, washed

1-Johnson, J.R., Org. Syn., 16, 89
twice with water, and the acidic material extracted with 5% sodium carbonate solution. Upon acidification with hydrochloric acid 173.3 g. (97%) of brown solid separated, m.p. 129-135°. Recrystallization from methanol gave 19 g. (10%) of the higher melting colorless racemate, m.p. 171.8-172.8°.

Analysis (c) Calcd. for C_{17}H_{18}O_2: C, 80.3 H, 7.1

    Found:               C, 80.5 H, 7.2
                         C, 80.7 H, 7.2

The mother liquor, upon addition of water, yielded colorless crystals, melting from 126° to 135°, presumably a mixture of lower and higher melting racemates. This mixture could not be further separated by recrystallization.

From the neutral benzene solution 4.8 g. of crystalline amide was obtained, m.p. 99-139°. Recrystallization from benzene produced colorless plates, m.p. 149.9-150.8°.

Analysis (c) Calcd. for C_{17}H_{19}ON: C, 80.6 H, 7.6

    Found:               C, 80.6 H, 7.2
                         C, 80.6 H, 7.1

\(\beta\)-o-Tolyl-\(\gamma\)-phenylvaleric acid (IIIa)(IIIb). In the best of many experiments the acid chloride was prepared by addition of 25.4 g. (0.1 mole) of the mixture of
racemates (II) to 23.8 g. (0.2 mole) of purified thionyl chloride, followed by intermittent shaking of the solution until the evolution of hydrogen chloride subsided (about two hours). The solution was warmed on the water bath at 45-50° for one half hour, and the excess thionyl chloride was removed under diminished pressure using a water pump. To insure removal of all residual thionyl chloride, 25 ml of dry thiophene-free benzene was added and evaporated by means of the water pump.

The dark brown acid chloride was dissolved in 50 ml of dry benzene and added dropwise to a rapidly stirred ice-cold ethereal solution of diazomethane prepared from 35 g. of N-nitroso-N-methylurea in 500 ml of ether. Stirring was continued for one hour after the addition was complete, and the solution was allowed to come to room temperature. The solvent was removed by use of the water pump, and the yellow oil was dissolved in 200 ml of absolute methanol. Addition of three portions of two milliliters each of a saturated solution of silver benzoate in dry triethylamine caused an immediate evolution of nitrogen, which continued progressively, with concomitant darkening of the solution, for about twenty minutes.
The methanolic solution was decolorized with decolorizing charcoal (Darco G-60), filtered, and the solvent removed. The residual oil was distilled to give 32.5 g. of the methyl ester, b.p. 146-156°/1.2 mm.

The ester was hydrolyzed by refluxing overnight with 70 ml of 10% alcoholic potassium hydroxide. The solution was acidified and extracted with ether, and after the solvent was stripped, the oil was dissolved in the least possible volume of Skellysolve F. From this solvent 20.2 g. (76.3%) of mixed crystals separated. These were manually segregated into the two racemates: (a) colorless needles, m.p. 113-120°

(b) colorless plates, m.p. 78-98°.

Recrystallization of (a) from petroleum ether, b.p. 95-100°, gave small needle-like crystals, m.p. 125.2-126.4°.

Analysis (c) Calcd. for C_{18}H_{20}O_{2}: C, 80.6 H, 7.5

\[ \begin{align*}
C, & \quad 80.7 \quad H, 7.4 \\
C, & \quad 80.5 \quad H, 7.4
\end{align*} \]

Recrystallization of (b) from Skellysolve F gave large plate-like crystals, m.p. 100.2-100.4°.

Analysis (c) Calcd. for C_{18}H_{20}O_{2}: C, 80.6 H, 7.5

\[ \begin{align*}
C, & \quad 81.1 \quad H, 7.5 \\
C, & \quad 80.8 \quad H, 7.4
\end{align*} \]

From the mother liquor 3.52 g. of brown oil was isolated.
3-o-Tolyl-4-methyl-1-tetralone (IVa)(IVb). To a mixture of 13 g. (0.0625 mole) of phosphorus pentachloride in 75 ml of dry thiophene-free benzene was added 13.4 g. (0.05 mole) of (IIIa). The mixture was stirred rapidly for twenty minutes. During the cooling of the mixture in an ice bath 26 g. (0.1 mole) of stannic chloride in 50 ml of dry benzene was added with vigorous stirring. Immediately a pale yellow complex separated. Stirring was continued for one hour in the cold, then for one hour at room temperature. The mixture was decomposed by the addition of 50 ml of ether, ice, and 75 ml of concentrated hydrochloric acid. The organic layer was washed successively with 10% hydrochloric acid, water, 5% potassium hydroxide, water, and saturated salt solution and dried with anhydrous sodium sulfate. Upon removal of the solvent, the residual oil was dissolved in ethanol, from which there was obtained 12.3 g. (98%) of crystalline material, m.p. 62-74°. Recrystallization from ethanol gave 11.1 g. (89%) of colorless crystalline solid, m.p. 72.6-73.4°.

Analysis (c) Calcd. for C_{18}H_{18}O(a): C, 86.4  H, 7.3

Found: C, 86.6  H, 7.2
A similar experiment with (IIIb) gave a 95\% yield of colorless solid from ethanol: 10.83 g. melting at 65-132\(^\circ\)C, and 1.06 g. melting at 70-74\(^\circ\)C. A sample of the colorless needles was purified for analysis by crystallization from ethanol and melted at 150.6-151.8\(^\circ\)C.

Analysis (c) Calcd. for C\(_{18}\)H\(_{18}\)O(b): C, 86.4  H, 7.3

Found:

\[
\begin{align*}
\text{C,} & \quad 85.7 \quad \text{H,} \quad 7.2 \\
\text{C,} & \quad 85.6 \quad \text{H,} \quad 7.0
\end{align*}
\]

2-Methylglyoxalate-3-o-tolyl-4-methyl-1-tetralone (Va)(Vb).

To a sodium methoxide solution, prepared from 6.9 g. (0.26 mole) of sodium and 60 ml of dry methanol, was added 18.75 g. (0.075 mole) of the high-melting (IVb), 27 g. (0.26 mole) of methyl oxalate and 300 ml of dry thiophene-free benzene in an atmosphere of dry nitrogen. The mixture was stirred with warming for one half hour, when solution was complete, and for twenty-four hours thereafter. During the latter period the color changed gradually from pale yellow to red. Water was added and the alkaline layer separated. The benzene solution was washed several times with 5\% sodium hydroxide. The combined alkaline extracts, after acidification with dilute hydrochloric acid, gave a yellow oil which became crystalline after standing overnight. Filtration yielded 24.13 g. (96\%) of yellow solid,
m.p. 99-107°. Yellow plates, m.p. 110.4-111.4°, were obtained from methanol.

Analysis (c) Calcd. for \( \text{C}_2\text{H}_{20}\text{O}_4 \): C, 75.0 H, 6.0

Found: C, 74.8 H, 6.4 C, 74.8 H, 6.2

A similar experiment using 24 g. of (IVa) gave 31.6 g. (94%) of yellow crystalline material, m.p. 110.4-111.0°. This substance gave a depressed mixed melting point with (Va).

Analysis (c) Calcd. for \( \text{C}_2\text{H}_{20}\text{O}_4 \): C, 75.0 H, 6.0

Found: C, 75.2 H, 5.8 C, 75.4 H, 6.0

2-Carbomethoxy-5-o-tolyl-4-methyl-1-tetralone (VI).

Decarbonylation of (V) was brought about by placing 35 g. (0.104 mole) of glyoxalate in a large Pyrex tube and immersing it in a salt bath at 165°. Then 10 g. (0.03 mole) of crushed Cargille boiling stones were stirred in with a glass rod under an atmosphere of dry nitrogen, and the temperature was allowed to rise slowly to 190°. When the evolution of carbon monoxide was complete (about one half hour), the cooled mass was stirred with benzene and filtered. The benzene was evaporated and the residual oil distilled. There was obtained 26.2 g. of oil, which crystallized from Skellysolve B to give 17.4 g. of
solid, 54%, m.p. 93-103°C, and 8.4 g. of semi-solid, total 80%. After purification by recrystallization from Skellysolve C, there was obtained 12.2 g. (38%) of crystalline material, m.p. 98.0-120.0°C.

Analysis (c) Calcd. for C_{20}H_{20}O_{3}: C, 77.8 H, 6.5

Found: C, 77.9 H, 6.2
c, 77.8 H, 6.3

3-o-Poly-4-methyl-1-tetralone-2-acetic acid (VIIa).

A. Alkylation using sodium methoxide as a base.

A solution of sodium methoxide was prepared from 2.3 g. (0.1 mole) of sodium and 100 ml of anhydrous methanol. To the methoxide was added 16.1 g. (0.0522 mole) of (VI), and the solution was refluxed for one hour. It was then cooled, and 15.3 g. (0.1 mole) of methylbromoacetate in 50 ml of dry benzene was added. The mixture was allowed to stand for one hour at room temperature with occasional shaking. Immediately sodium bromide separated. The mixture was refluxed for one-half hour, cooled, and poured into ice water, after which it was extracted with benzene. The organic extract was washed with water and with saturated salt solution, then dried with anhydrous sodium sulfate. After the solvent had been removed, the oil was refluxed for three hours
with 100 ml of glacial acetic acid, 50 ml of hydrochloric acid, and 7 ml of water. The hydrolysate was poured into 300 ml of water and extracted with benzene. After the organic layer had been washed twice with water, the acidic material was extracted with 5% sodium hydroxide and acidified. Recrystallization of the resultant oil from benzene gave:

(a) 0.9 g solid material, melting from 210 to 220°
(b) 2.8 g solid material, melting from 161 to 167°.

When (a) was recrystallized from benzene it melted at 215.3-217.0°.

Analysis Calcd. for C_{20}H_{20}O_3: C, 77.8 H, 6.5

Found: C, 78.1 H, 6.4
C, 78.0 H, 6.5

When (b) was recrystallized from benzene it melted at 174.6-176.4°. On the basis of the analysis it was presumed to be the half-ester resulting from partial hydrolysis without decarbonylation, (XIII).

Analysis Calcd. for C_{22}H_{22}O_5: C, 72.1 H, 6.1

Found: C, 72.5 H, 6.0
C, 72.5 H, 6.3

B. Alkylation using potassium t-butoxide as base (VIIb).

To a cooled solution of potassium t-butoxide, prepared from 1.4 g. (0.036 mole) of potassium and 60 ml of
dry t-butyl alcohol, was added 5 g. (0.0162 mole) of the keto ester (VI) in 25 ml of dry benzene. The solution was refluxed on the steam bath for two hours, cooled in an ice bath, and treated with 5.5 g. (0.036 mole) of methyl bromoacetate. The solution was shaken intermittently for one half hour at room temperature, refluxed on the steam bath for three hours, cooled, and finally acidified with concentrated hydrochloric acid. The solvent was removed by means of the water pump, and the residual oil was heated on the steam bath for three hours with 50 ml of glacial acetic acid, 50 ml of hydrochloric acid, and 5 ml of water. The solution was then poured into water and extracted with benzene, from which the acidic material was obtained by extraction into 5% sodium hydroxide and subsequent acidification. The crude acid was obtained in 61.5% yield (3.07 g.), melting from 154 to 176°. Recrystallized from benzene, the acid was found to melt from 190.0 to 199.0°.

Analysis (b) Calcd. for C₂₀H₂₉O₃: C, 77.9 H, 6.5

Found: C, 78.4 H, 6.8
        C, 78.2 H, 6.9

C. Reduction of the glyoxalate with sodium amalgam¹ (VIIb).

¹-Erlenmeyer, Ber., 35, 3767 (1902)
During the stirring of a suspension of 5 g. (0.0149 mole) of the glyoxalate (V) in 150 ml of ethanol, 50 g. of 4% sodium amalgam was added. Stirring was continued until the amalgam disintegrated, leaving pure mercury on the bottom of the flask. Then stirring was allowed to continue for one hour after an additional 25 g. of the amalgam had been added. The supernatant liquid was decanted through filter paper from the mercury, and the solvent was removed. The oil was refluxed overnight with 50 ml of glacial acetic acid, 50 ml of hydrochloric acid, and 5 ml of water. It was then poured into water and extracted with 5% sodium hydroxide. Upon acidification of the alkaline extract there was obtained 1.23 g. (20%) of brown solid, melting from 174 to 192°. When recrystallized from benzene it melted at 196.8-199.0°.

Analysis (c) Calcd. for C_{20}H_{20}O_{5}: C, 77.9 H, 6.5
            Found:             C, 78.0 H, 6.5
                        C, 77.8 H, 6.5

D. Reduction of the glyoxalate with sodium borohydride (VIIc).

A cold solution of 6.72 g. (0.02 mole) of glyoxalate (V) in 50 ml of methanol was added dropwise
to a solution of 4 g. of sodium borohydride in 100 ml of methanol at a temperature of -78°. When the addition was complete the solution was acidified cautiously with hydrochloric acid. The methanol then was removed and the residue refluxed overnight with 50 ml of glacial acetic acid, 50 ml of hydrochloric acid, and 5 ml of water. The solution was poured into water and extracted with benzene. The acidic material was removed with 5% sodium hydroxide and acidified. There resulted 1.66 g. (27%) of solid, m.p. 164.0-166.0°.
The colorless solid, recrystallized from benzene, melted sharply at 164.2-165.0°.
Analysis (b) Calcd. for C$_{20}$H$_{20}$O$_3$: C, 77.9 H, 6.5
Found: C, 77.5 H, 6.3

1,2,3,4-Tetrahydro-3-o-tolyl-4-methyl-2-naphthyl acetic acid (X). To a cold mixture of 5 g. of freshly fused zinc chloride, 4 g. of anhydrous sodium sulfate, and 85 ml of ethyl mercaptan was added 5 g. (0.015 mole) of glyoxalate (V). The mixture was swirled continually until all of the zinc chloride had gone into solution, whereupon it was allowed to stand overnight in the ice chest. After four hours at room temperature the mixture was poured into an ice-ether mixture in a separa-
tory funnel and washed successively with 5% potassium hydroxide, water, and saturated salt solution and dried with anhydrous sodium sulfate. When the ether was evaporated there remained 6.89 (98%) of dark brown oil.

The oil in 500 ml. of ethanol was refluxed overnight with 150 g. of Raney nickel. After filtration and thorough washing of the nickel with hot benzene, the solvent was removed and the solution concentrated to give 1.92 g. (61%) of light brown oil.

A mixture of 1.9 g. of the oil, 100 ml of glacial acetic acid, 120 g. of amalgamated zinc, 120 ml of concentrated hydrochloric acid, and 25 ml of toluene was refluxed for thirty hours. During this period an additional 300 ml of hydrochloric acid was added. The toluene layer was separated and the aqueous material extracted with benzene. The acidic material was extracted with 5% potassium hydroxide, from which acidification yielded 1.25 g. (65.5%) of oil. Crystallization from benzene gave 1.1 g. of colorless solid, melting from 130 to 162°, which could not be purified further.

1',9-Dimethyl-3,10-diketo-3,4,4a,9,9a,10-hexahydro-1,2-benzanthracene (VIII). A mixture of 1.0 g.

1-Fieser and Kilmer, J. Am. Chem., 61, 864 (1939)
(0.00325 mole) of (VIIb)(m.p. 197-199°), 16 g. of oxalyl chloride, and 30 ml of dry benzene was allowed to react for four hours. With cooling in ice water there was added 16 g. of stannic chloride in 20 ml of benzene, and the mixture was swirled vigorously for ten minutes. Ice and 30 ml of hydrochloric acid were added and the benzene layer removed. This was washed successively with hydrochloric acid, water, alkali, and saturated salt solution and then dried with anhydrous sodium sulfate. After evaporation of the solvent there remained an oil which was taken up in ethanol, from which crystallized 0.4 g. (53% based on recovered acid) of yellow solid, m.p. 176-177°, with sintering at 172°. A sample recrystallized for analysis from ethanol melted sharply at 178.6-179.6°.

Analysis (c) Calcd. for C_{20}H_{18}O_2: C, 82.7  H, 6.3

Found: C, 82.8  H, 6.4

C, 82.7  H, 6.2

From the alkaline extracts there was obtained 0.2 g. of acidic material, m.p. 195-198°.
A partial synthesis of 1',9-dimethyl-1,2-benzanthracene has been described.

The condensation of α-bromoethylbenzene with o-tolylacetonitrile was effected in good yield giving α-o-tolyl-β-phenylbutyronitrile.

Acid hydrolysis of the nitrile afforded excellent yields of α-o-tolyl-β-phenyl butyric acid. The higher melting racemate was isolated pure.

Homologation of the mixture of acid racemates via the Newman-Beal modification of the Arndt-Eistert reaction yielded the two racemates of β-o-tolyl-γ-phenyl valeric acid in good yield.

Cyclization of these acids gave the two racemates of 3-o-tolyl-4-methyl-l-tetralone in nearly quantitative yield.

Reaction of the cyclic ketone with dimethyl oxalate in the presence of sodium methoxide gave the corresponding glyoxalate.

Reduction of the glyoxalate with sodium amalgam and with sodium borohydride and hydrolysis of the intermediate α-hydroxy lactone gave small amounts of the desired keto acid, 3-o-tolyl-4-methyl-l-tetralone-2-acetic acid.

The glyoxalate was decarbonylated smoothly.
at 180° to 2-carbomethoxy-3-o-tolyl-4-methyl-1-tetralone in the presence of Cargille boiling chips.

This β-keto ester was alkylated with methyl bromoacetate and the product hydrolyzed and decarboxylated to the keto acid, 1-keto-2-carboxymethyl-3-o-tolyl-4-methyl-1,2,3,4-tetrahydronaphthalene in fair yield.

This keto acid was cyclized by way of its acid chloride to give the diketone, 1',9-dimethyl-3,10-diketo-3,4,4a,5,9,9a-hexahydro-1,2-benzanthracene in 53% yield.
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