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THE SYNTHESIS AND RESOLUTION OF
1-FLUORO-12-METHYLBENZO(C)PHENANTHRENE

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Robert George Mentzer, B.S.

*****

The Ohio State University
1962

Approved by

[Signature]
Adviser
Department of Chemistry
ACKNOWLEDGMENT

I wish to extend to Professor Melvin S. Newman my deepest gratitude for his suggestion of this problem and for his advice and encouragement. His warm friendship was sincerely appreciated throughout the duration of this work.

I would also like to thank, at this time, The Ohio State University, the National Science Foundation, and the United States Public Health Service for their assistance during the time I was in Graduate School.
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</tbody>
</table>
INTRODUCTION

Uniplanarity is a well-established characteristic of many polynuclear aromatic hydrocarbons.\(^1,2\)


However, there are a number of polynuclear aromatic hydrocarbons termed "overcrowded" by Bell and Waring\(^3\) which are


forced into nonplanar configurations due to intramolecular repulsion between nonbonded atoms.

The possibility that optical activity might be found in compounds of this type was first pointed out in 1940.\(^4\) In particular, it was predicted that molecules containing


the 4,5-dimethylphenanthrene system (I) might be optically active due to the effect of the interference of the methyl groups in the hindered positions. Three alternatives were suggested as to the geometry of the molecule.
"1) The methyl groups lie bent away from each other but in the same plane as the aromatic ring; 2) The aromatic rings are distorted in some way; 3) The methyl groups are bent out of the plane of the aromatic rings". If the first alternative is correct, there would be no asymmetry and the molecule would not be optically active. However, if the second or third alternative, or a combination of the two, is correct, the molecule might contain no element of symmetry and would be optically active.

That 2) or 3) is the correct explanation has been shown by the successful resolution of \( \text{II} \), \( \text{III} \), and \( \text{IV} \), and of the other overcrowded molecules, \( 1-(1\text{-methylbenzo-(c)phenanthryl acetic acid (III)}} \); \( 1, 1', 6, 6'\text{-tetramethyl-3,4,5,6-dibenzophenanthrene-9,10-dicarboxylic acid (IV)}} \); and \( 1,12\text{-dimethylbenzo(c)phenanthrene-5-acetic acid (V)}} \).

(7) F. Bell and D. Waring, J. Chem. Soc., 2689 (1949)

Compounds II and III racemize fairly readily at room temperature. The stability of compound IV at room temperature was not stated but on warming for 1 hour at 60°C in methanol it racemized completely. Compound V is optically stable at temperatures well
over 200°. When racemization commences near 250° decomposition also sets in.

X-ray crystallographic investigation has established that aromatic rings may be rendered nonplanar because of internal strain. The structure of benzo(c)phenanthrene as determined by X-ray diffraction in the solid state is shown (Figure 1, No. VI).


The determination shows bond angles of 110° at carbons 3 and 10, and 111° at carbons 5 and 8. Thus, the tetrahedral angle of 109-1/2° is approached. This implies that the pi electrons of these secondary atoms do not occupy pure (sp²)p orbitals, but occupy orbitals more nearly approximate to the tetrahedral sp³ hybridization; thus implying a greater localization of the pi electrons at these atoms. This view would explain, in part, the preferential attack of electrophilic agents at the 5 position.

Figure 1
STATEMENT OF THE PROBLEM

All of the polynuclear hydrocarbon derivatives possessing optical activity due to intramolecular overcrowding prepared thus far either racemize readily at room temperature or are optically stable up to the decomposition temperature. If a compound could be prepared that was optically stable at room temperature but racemized readily at higher temperatures, a study of the rate of racemization of the active compound at different temperatures could be made. From these observed rates the activation energy and the entropy of activation for the racemization could be calculated.

In view of the fact that the 1-methylbenzo(c)phenanthrene derivative racemizes readily at room temperature while the 1,12-dimethyl is optically stable, it was felt that 1-fluoro-12-methylbenzo(c)phenanthrene might possess the desired properties.

Thus, the purpose of this work was to synthesize 1-fluoro-12-methylbenzo(c)phenanthrene and, if possible, to study its rate of racemization at several different temperatures in order to calculate the activation energy and the entropy.

In addition, since the benzo(c)phenanthrenes are carcinogenic compounds, the racemie, (+), and (-) compounds could be tested to see if there is any difference in activity.
OUTLINE OF BENZO(C)PHENANTHRENE SYNTHESSES

The synthetic routes to the benzo(c)phenanthrene ring system have been reviewed by Kosak (through 1947),\textsuperscript{1} by Wolf (through 1950),\textsuperscript{2} by Wise (through 1954),\textsuperscript{3} and by Phillips (through 1956).\textsuperscript{4}

(1) A. Kosak, Ph.D. Dissertation, The Ohio State University, 1948

(2) M. Wolf, Ph.D. Dissertation, The Ohio State University, 1951

(3) R. Wise, Ph.D. Dissertation, The Ohio State University, 1955


Further syntheses of this system (through Chemical Abstracts, 1960), are outlined below.

The synthetic route used by the Newman group\textsuperscript{2,3,4} forms the basis for the present research and will be discussed in another section.

The cyclization\textsuperscript{5} with anhydrous hydrogen fluoride of trans-2-\(\alpha\)-naphthylcyclohexanacetic acid (I, Figure 2), afforded a 60 per cent yield of trans-6-keto-1,2,3,4,5,6,13a-octahydrobenzo (c)phenanthrene (II). A Reformatsky reaction on the ketone (II) afforded ethyl trans-1,2,3,4,5,6,13a-octahydro-6-benzo(c)-phenanthrylidene acetate (III), in 97 per cent yield. Subsequent
Figure 2

\[
\begin{align*}
\text{I} & \xrightarrow{\text{HF, 60\%}} \text{II} \\
\text{II} & \xrightarrow{97\% \text{ BrCH}_2\text{CO}_2\text{Et}, \text{Zn}} \text{III} \\
\text{III} & \xrightarrow{\text{70\%, 1. Hydrolysis}} \text{IV} \\
\text{IV} & \xrightarrow{\text{I.W.K., 2. Pd/C, 7\%}} \text{V}
\end{align*}
\]

Figure 3

\[
\begin{align*}
\text{I} & \xrightarrow{\phi(\text{CH}_2)_2\text{Br, NaNH}_2, 34\%} \text{II} \\
\text{II} & \xrightarrow{34\%, 1. LiAlH}_4} \text{III} \\
\text{III} & \xrightarrow{\text{Pd/C, 72\%}} \text{IV}
\end{align*}
\]
hydrolysis, hydrogenation, and cyclization yielded 1-keto-4,5-tetramethylene-6,7-benzo-2a,3,4,5-tetrahydro-acenaphthene (IV) in 70 per cent yield. Wolf-Kishner reduction and dehydrogenation over palladium-on-charcoal afforded 6,7-acebenzo(c)phenanthrene (V) in 7 per cent yield.


A new synthesis of 2-methylbenzo(c)phenanthrene starting from 7-methyltetralone has been reported. The tetralone (I, Figure 3) was reacted with p-phenylethylbromide to give 7-methyl-2-(p-phenylethyl)-tetralone (II) in 31 per cent yield. Reduction of (II) to the alcohol followed by cyclization gave a 31 per cent yield of 2-methyl-5,6,6a,7,8,12b-hexahydrobenzo(c)phenanthrene (III). On treatment with palladium-on-charcoal, 2-methylbenzo(c)phenanthrene was obtained in 72 per cent yield.


A new synthesis of 5-methylbenzo(c)phenanthrene has been reported starting with allylsuccinic anhydride (I, Figure 4). Friedel-Crafts reaction between this anhydride and benzene afforded, among other products, a 14 per cent yield of methyl-α-phenacyl-γ-phenylvalerate (II). Saponification followed by reduction of the ketone function afforded the acid (III) in
CH\_2-CH\_2-CH\_2-CH-\text{C}=O & AlCl\_3 & 14\% \\
\text{CH}^-\text{C}^s & 14\% \\
1. \text{Saponification} & 87\% \\
2. \text{H}_2 \\

\text{I} \quad \text{II} \\

\text{PCl}_5 & 1. \\
\text{AlCl}_3 & 2. \\
97\% \\

\text{III} \\

\text{LiAlH}_4 & 1. \\
\text{H}_2\text{SO}_4 & 2. \\
62\% \\

\text{IV} \\

\text{Pd/C} & 45\% \\

\text{V} \\

\text{VI} \\

Figure 4
87 per cent yield. Friedel-Crafts cyclization of the acid then
gave a 97 per cent yield of 2-(β-phenylpropyl)-1-tetralone (IV)
and/or 2-(β-phenylethyl)-1-methyl-1-tetralone. Lithium aluminum
hydride reduction of this tetralone mixture, followed by
cyclization, afforded 5-methyl-5,6,6a,7,8,12a-hexahydrobenzo(c)-
phenanthrene in 62 per cent yield. Aromatization over
palladium-on-charcoal afforded 5-methylbenzo(c)phenanthrene (VI),
in 45 per cent yield.

(7) D. Phillips and T. Hill, J. Amer. Chem. Soc., 80,
3663 (1958)
DISCUSSION OF RESULTS

The plan for the synthesis of 1-fluoro-12-methylbenzo(c)-phenanthrene was to employ the method (Figure V) of Newman and Wolf as further modified. 

(3) M. S. Newman and D. Lednicer, J. Amer. Chem. Soc., 78, 4765 (1956)

o-Fluorobenzaldehyde was condensed with diethyl malonate to form diethyl o-fluorobenzalmalonate (II) in 94 per cent yield.

Addition of o-tolylmagnesium bromide to diethyl o-fluorobenzal-malonate afforded diethyl 2-fluoro-2'-methylbenzhydrylmalonate (III) in 83 per cent yield. Normal addition lowered the yield to 76 per cent. The presence of 2 mole per cent of cuprous chloride in the benzalmalonate solution seemed to have no effect on the yield in either case.

Figure 5
Lithium aluminum hydride reduction of diethyl 2-fluoro-2'-methylbenzhydrylmalonate (III) to 2-(2-fluoro-2'-methylbenzhydryl)-1,3-propanediol (IV) proceeded readily. Trituration of the crude reaction product with petroleum ether gave white solid diol (IV), in 91 per cent yield.

The mesylation of the diol (IV) to produce 2-(2-fluoro-2'-methylbenzhydryl)-1,3-propanediol-bis(methanesulfonate) (V) afforded crude product in yields of 90 per cent.

The conversion of the methanesulfonate ester (V) to 3-(2-fluoro-2'-methylbenzhydryl)glutaronitrile (VIA) proceeded in about 94 per cent yield.

The dinitrile (VIA) could then be readily hydrolyzed to the 3-(2-fluoro-2'-methylbenzhydryl)glutaric acid (VIB) in 93 per cent yield.

Conversion of diethyl 2-fluoro-2'-methylbenzhydrylmalonate to 3-(2-fluoro-2'-methylbenzhydryl)glutaric acid, without isolation of the intermediates proceeded in 69 per cent overall yield. Thus, the four steps went in on average yield of 91.5 per cent.

The double cyclization of the glutaric acid derivative (VIB) to 6a,12b-dihydro-1-fluoro-12-methylbenzo(c)phenanthrene-5,8(6H,7H)-dione (VII) gave difficulty. With polyphosphoric acid the maximum yields of crude red neutral oil were 60-65 per cent. However, crystallization yielded a single crystalline diketone (VII) in only 30-44 per cent yield, the residue remaining as a viscous red gum.
(6) Since the diketone has two asymmetric centers there should be two dl pairs, a cis, and a trans relative to the 6a and 12b hydrogens. However, if there is sufficient steric hindrance between the fluorine and the methyl groups to prevent them from flipping past each other, then each isomer will, in addition, be frozen into either a right- or left-handed helix. Thus, there is a possibility for 4 dl pairs.

The remainder of the reaction product was isolated either as keto-acid\textsuperscript{7} or black insoluble tar.

(7) During the course of this work, only one keto-acid isomer was isolated. It is not known whether the 6a and 12b hydrogens are cis or trans, or whether the keto-acid is isomer X or XI.

\[ \text{X} \]

\[ \text{XI} \]
Isomer XI is favored in view of the fact that the corresponding 1,12-dimethyl glutaric acid derivative, on treatment with polyphosphoric acid, is converted to the corresponding diketone in 89 per cent yield with recovery of 9 per cent of starting diacid. Thus, the major effect preventing the second ring closure appears to be the deactivation of the meta position by the fluorine.

The reaction was very unpredictable and supposedly similar runs often gave widely varying proportions of product. However, if one observed the color of the reaction mixture as it darkened from tan to brown to dark brown to black, and stopped the reaction at the dark brown stage, yields in the 40-44 per cent range could be obtained regularly.

Cyclization attempts using anhydrous hydrofluoric acid at its boiling point (19°C) gave the same keto-acid in high yield (97 per cent). Reactions employing anhydrous hydrofluoric acid in a bomb at 60°C also failed to yield the desired diketone.

Attempts to prepare the diacid chloride using either phosphorus pentachloride or thionyl chloride resulted in formation of the anhydride.

Since the keto-acid was available in high yield by use of anhydrous hydrofluoric acid, attempts were made to cyclize its acid chloride by use of stannic or aluminum chloride. Here again,
moderate yields of neutral gum were obtained, but crystallization lowered the yield to 30-35 per cent of an isomeric diketone which was not further investigated.

Reduction of the diketone (VII) with lithium aluminum hydride gave a wide melting solid which is apparently a mixture of stereoisomeric diols. Recrystallization was difficult and sharp melting samples could not be obtained. However, treatment with ethyl chloroformate yielded a sharp melting derivative (XII).

Previous work had shown that diols similar to VIII, but with different substituents in the 1 and 12 position, could be converted directly to the benzo(c)phenanthrene by refluxing in xylene with a trace of iodine for over 100 hours.

Upon similar treatment the diol mixture (VIII) yielded 1-fluoro-12-methylbenzo(c)phenanthrene directly in 90 per cent yield.

Thus, 1-fluoro-12-methylbenzo(c)phenanthrene has been synthesized from o-fluorobenzaldehyde in 9.2 per cent overall yield. (I to II, 94 per cent; II to III, 83 per cent; II to IV, 91 per cent; IV to V, 90 per cent; V to VI, 94 per cent; VI to VII, 92 per cent; VII to VIII, 92 per cent; VIII to IX, 90 per cent.)

The fully aromatic character of IX was shown by the following:

(1) Microanalytical data corresponded more closely to $\text{C}_{15}\text{H}_{13}\text{F}$ than to $\text{C}_{15}\text{H}_{15}\text{F}$.

(2) The compound formed a 2,4,5,7-tetranitrofluorenone complex which gave the analytical values expected for a 1:1 complex.

(3) The ultraviolet absorption spectrum (Figure VI) agreed closely with those of known benzo(c)phenanthrene derivatives.\(^9\)

---


---

\(^10\) The nuclear magnetic resonance spectrum agreed with the proposed structure. There appeared a number of peaks in the 2.0 to 3.0 ppm region (aromatic hydrogen). The only other peak was a doublet at 7.68 ppm, with a coupling constant of 2.2 cps. This is attributed
Fig. 6. — Ultraviolet absorption spectra. (a) 1-fluoro-12-methylbenzo(c)phenanthrene, (b) 1,12-dimethylbenzo(c)phenanthrene. (lowered .25 log units)
<table>
<thead>
<tr>
<th>Wavelength (μm)</th>
<th>Log ε</th>
<th>Wavelength (μm)</th>
<th>Log ε</th>
</tr>
</thead>
<tbody>
<tr>
<td>212</td>
<td>4.32  (min.)</td>
<td>215</td>
<td>4.46  (min.)</td>
</tr>
<tr>
<td>221</td>
<td>4.55  (max.)</td>
<td>224</td>
<td>4.60  (max.)</td>
</tr>
<tr>
<td>210</td>
<td>4.05  (min.)</td>
<td>214</td>
<td>4.07  (min.)</td>
</tr>
<tr>
<td>248</td>
<td>4.10  (max.)</td>
<td>250</td>
<td>4.08  (max.)</td>
</tr>
<tr>
<td>255</td>
<td>4.09  (min.)</td>
<td>254</td>
<td>4.05  (min.)</td>
</tr>
<tr>
<td>289</td>
<td>4.73  (max.)</td>
<td>292</td>
<td>4.78  (max.)</td>
</tr>
<tr>
<td>322</td>
<td>3.87  (min.)</td>
<td>324</td>
<td>3.91  (min.)</td>
</tr>
<tr>
<td>326</td>
<td>3.88  (max.)</td>
<td>328</td>
<td>3.92  (max.)</td>
</tr>
<tr>
<td>361</td>
<td>2.49  (min.)</td>
<td>363</td>
<td>2.46  (min.)</td>
</tr>
<tr>
<td>367</td>
<td>2.51  (max.)</td>
<td>370</td>
<td>2.50  (max.)</td>
</tr>
</tbody>
</table>
Determined by Dr. George Slomp, The Upjohn Co., Kalamazoo, Michigan

to the aromatic methyl group which has been split by the fluorine. This splitting by a nearby fluorine has been noted before.\(^\text{11}\)

Dr. Slomp reports (unpublished results) Compound XIII also has its methyl group split into a doublet \((J = 1.5 \text{ cps.})\).

\[
\text{XIII}
\]

The 1-fluoro-12-methylbenzo(c)phenanthrene was successfully resolved by use of the optically active complexing agent \((-\text{a-} (2,4,5,7\text{-tetranitro-9-fluorenylid})\text{propionic acid.}\)\(^\text{12}\)

The resolved material had \([\alpha]_D^{25^\circ} = \pm 580^\circ\) in chloroform (C=0.005 g./ml.). The compound was optically stable at room temperature and did not begin to racemize at an appreciable rate until a temperature of 80-90\(^\circ\) was reached.

The optical rotatory dispersion curve is shown in Figure VII along with that of 1,12-dimethylbenzo(c)phenanthrene-5-acetic acid.\(^{13}\)

\(^{(13)}\) Determined by Dr. Stanley M. Bloom, Polaroid Corp., Cambridge 39, Massachusetts

The curve for the 1-fluoro-12-methylbenzo(c)phenanthrene was run on a Rudolph continuous recording spectropolarimeter. Light absorption seriously limited the accuracy below 400 \(\mu\) and eventually made further readings impossible.

The rates of racemization were measured in duplicate at 3 convenient temperatures. The results are tabulated in Table 3 and are plotted in Figures VIII, IX, and X.\(^{14}\)

\(^{(14)}\) The kinetics obey the rate law:

\[
\ln \frac{\alpha_1}{\alpha_2} = 2k \left( t_1 - t_2 \right)
\]

\(\alpha = \) observed rotation

\(t = \) time

For a derivation, see D. Smith, J. Amer. Chem. Soc., 49, 43 (1927)

Good straight line plots of log \(\alpha\) versus time were obtained from which the rate constants were calculated.
Fig. 7 – Optical rotatory dispersion.

a. 1-fluoro-12-methylbenzo(c)phenanthrene,
b. 1,12-dimethylbenzo(c)phenanthrene-5-acetic acid
<table>
<thead>
<tr>
<th>Wavelength (m\textmu)</th>
<th>(\alpha)</th>
<th>Wavelength (m\textmu)</th>
<th>(\alpha)</th>
</tr>
</thead>
<tbody>
<tr>
<td>640</td>
<td>-570</td>
<td>585</td>
<td>-230</td>
</tr>
<tr>
<td>610</td>
<td>-620</td>
<td>546</td>
<td>-240</td>
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<td>580</td>
<td>-700</td>
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<td>-890</td>
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<td>475</td>
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<td>430</td>
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<td>436</td>
<td>-250</td>
</tr>
<tr>
<td>400</td>
<td>-1580</td>
<td>420</td>
<td>-150</td>
</tr>
<tr>
<td>385</td>
<td>-1650</td>
<td>406</td>
<td>+140</td>
</tr>
<tr>
<td>370</td>
<td>-1640</td>
<td>366</td>
<td>+2000</td>
</tr>
<tr>
<td>360</td>
<td>-1300</td>
<td>355</td>
<td>+4200</td>
</tr>
<tr>
<td>355</td>
<td>0</td>
<td>350</td>
<td>+700</td>
</tr>
<tr>
<td>352</td>
<td>+370</td>
<td>349</td>
<td>-2500</td>
</tr>
</tbody>
</table>
Fig. 8. - Rate of racemization of 1-fluoro-12-methylbenzo(c) phenanthrene

91.7°
Fig. 9 - Rate of racemization of 1-fluoro-12-methylbenzo (c)phenanthrene
109.7°
Fig. 10.—Rate of racemization of 1-fluoro-12-methylbenzo(c)phenanthrene

$130.6^\circ$
Fig. 11. - Activation energy of 1-fluoro-12-methylbenzo (c)phenanthrene.
Table 3

RATES OF RACEMIZATION OF (-)-1-FLUORO-12-METHYLBENZO(C)PHENANTHRENE

<table>
<thead>
<tr>
<th>Temp.</th>
<th>Time (min.)</th>
<th>$\alpha$ (-deg.)</th>
<th>$k$ (sec. $^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>130.6°</td>
<td>0</td>
<td>4.29</td>
<td>7.90x10$^{-5}$</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>3.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>2.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>1.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>118</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td></td>
<td>210</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>310</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>130.4°</td>
<td>0</td>
<td>2.29</td>
<td>7.73x10$^{-5}$</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>1.71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>150</td>
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The values of log k versus 1/T were then plotted (Figure XI) to yield an excellent straight line. From the slope the activation energy was calculated to be 31.1 kcal/mole. \(^{15}\)

The statistical error was calculated to be .2 kcal/mole. \(^{16}\)

This value appears quite reasonable since reactions which are slow at room temperature exhibit activation energies of 20-30 kcal/mole. The entropy of activation was also calculated for the temperature 109.7\(^\circ\) and found to be \(-2.80 \text{ cal.} \pm .6 \text{ cal.} \) \(\text{deg.mole} \) \(\text{deg.mole} \). Thus, it appears that the transition state is only slightly more rigid than the reactant.
EXPERIMENTAL

Generalizations

1. All melting points are uncorrected unless otherwise stated.

2. Microanalyses were by either Galbraith Microanalytical Laboratories, Knoxville, Tennessee (designated "G"), or Schwarzkopf Microanalytical Lab., Woodside, New York, (designated "S").

3. The phrase, "treated in the usual manner" used throughout this section means that the organic solvent layer was washed successively with water and saturated sodium chloride solution, filtered through anhydrous magnesium sulfate, and the solvent distilled under reduced pressure. The term ether-benzene refers to approximately a 1:1 mixture (by volume) of diethyl ether and benzene.

4. Infrared spectra were recorded either on a Baird double-beam spectrophotometer or a Perkin-Elmer Infracord. A letter w, m, or s in parentheses following the wavelength indicates the intensity of the band as weak, medium, or strong respectively.

Diethyl o-Fluorobenzalmonate (II)$^1$

A mixture of 156 g. (1.25 moles) of o-fluorobenzaldehyde (Columbia Organic Chemical Company), 750 ml. benzene, 270 g. (1.69 moles) of diethyl malonate (Eastman White Label), 7.2 g. of benzoic acid, and 8.1 ml. of piperidine was placed in a 2-liter flask equipped with a 40 cm. column (Vigreaux) and phase-separating head and was refluxed under nitrogen for 11 hours. An additional 2 ml. of piperidine was added and the solution refluxed for 8 hours. At the end of this time 22.5 ml. (100 per cent) of water had separated. The clear, golden-brown solution was washed with water, 2N hydrochloric acid, and treated in the usual manner. Distillation afforded 316 g. (94 per cent) of chartreuse oil, b.p. 112-116° at 1 mm., after a forerun of 77 g., b.p. 63-64°. The infrared spectrum showed bands at 5.83 μ (s) (CO₂R), and 6.13 μ (s) (C=O).

A sample was distilled twice to yield a colorless liquid, nₒ² 1.5158.

Anal. (S) Calculated for C₁₄H₁₅FO₄:  C, 63.2; H, 5.7; F, 7.1
   Found:  C, 63.4; H, 5.7; F, 6.9

2-(2-Fluoro-2'-Methylbenzhydryl)-1,3-Propanediol (IV)

To a well-stirred solution of 53.2 g. (0.2 moles) of diethyl o-fluorobenzalmalonate, b.p. 112-116° at 1 mm., and 125 ml. of dry ether cooled to 0° was added dropwise, during 40 minutes a
solution prepared by adding 42 g. (0.24 moles) of o-bromotoluene in 150 ml. dry ether to 50 ml. of ether and 6.4 g. (.26 moles) of magnesium. The dark solution was refluxed for 1 hour and then hydrolyzed by addition of 150 ml. of 2N hydrochloric acid. The organic layer was separated and the aqueous layer washed with ether-benzene. The combined organic layers were washed with 10 per cent potassium carbonate solution and treated in the usual manner. Distillation yielded 59.6 g. (83 per cent) of a light-green oil, b.p. 192-200° at 1 mm.

A solution of 19.3 g. (0.0544 moles) of the light-green oil, b.p. 192-200° at 1 mm. in 75 ml. of dry ether was added to a well-stirred mixture of 4.6 g. (0.11 moles) of lithium aluminum hydride and 200 ml. of dry ether under nitrogen at a rate sufficient to maintain gentle reflux. After the addition was complete (1 hour) the mixture was refluxed for 6 hours. The excess hydride was decomposed by the careful dropwise addition of water and the mixture poured into 350 ml. of 10 per cent sulfuric acid, containing 100 g. of ice. The two layers were separated and the aqueous layer extracted with ether-benzene. The combined organic layers were washed with 10 per cent potassium carbonate solution and treated in the usual manner. Distillation afforded 11.1 g. (75 per cent) of a very viscous, almost colorless, liquid, b.p. 190-200° at 0.5 mm. The infrared spectrum showed a band at 2.9 μ (s) (OH) and no band near 5.8 μ.
On treatment with Skellysolve B, a white, poorly crystalline solid precipitated. Several recrystallizations from Skellysolve B-benzene afforded a white crystalline analytical sample, m.p. 78.5-80.0°.

Anal. (S) Calculated for C_{17}H_{19}F_{2}: C, 74.4; H, 7.0; F, 6.9
Found: C, 74.5; H, 6.8; F, 6.8

3-(2-Fluoro-2'-Methylbenzhydryl)-glutaric Acid (VI)

To a solution of 9.5 g. (.034 moles) of 2-(2-fluoro-2'-methylbenzhydryl)-1,3-propanediol, (b.p. 190-200° at 0.5 mm.) in 80 ml. dry pyridine cooled to -5° was added dropwise, with stirring, in 30 minutes, 13.8 g. (.12 moles) of methanesulfonyl chloride (Eastman White Label). After addition was complete, the stirring was stopped and the mixture was allowed to stand in the cooling bath for 4 hours. A large amount of solid, assumed to be pyridine hydrochloride, precipitated during this time. The light-orange mixture was poured into 250 ml. of cold water and stirred well. A yellow oil settled to the bottom of the flask and slowly solidified on standing for several hours. The solution was allowed to stand overnight and then filtered and washed with 1N hydrochloric acid and then water. The solid was dried overnight under vacuum to yield 14.2 g. (95 per cent) of the bis-(methanesulfonate) (V) as an almost white powder. The infrared spectrum (potassium bromide wafer) showed no band near 2.9 μ.
A solution of 13.4 g. (0.03 moles) of the crude bis-(methanesulfonate) (V), in 100 ml. of technical dimethylformamide, was added to a solution of 9.8 g. (0.15 moles) of potassium cyanide and 0.25 g. of potassium iodide in 60 ml. of water. Upon warming, and addition of 25 ml. of dimethylformamide, the mixture became homogeneous. After stirring at 87-92\(^\circ\) for 1-1/2 hours, the orange solution was allowed to cool to 60\(^\circ\) and then poured into 500 ml. of ice and water. A light reddish-brown precipitate formed immediately. The mixture was stirred well and then filtered. The precipitate was washed with water and dried to yield 8.6 g. (95 per cent) of crude dinitrile. The infrared spectrum showed a sharp band at 4.5 \(\mu\) (m) (C=CN).

A mixture of 8 g. (0.027 moles) of the crude dinitrile, 7 g. of sodium hydroxide, and 75 ml. ethylene glycol was heated, with occasional swirling, to the reflux temperature during which time the dinitrile and sodium hydroxide dissolved. The condenser was then removed until the temperature rose to 180\(^\circ\). After a few minutes a tan precipitate appeared and, in a very short period of time, filled most of the flask. An additional 20 ml. of ethylene glycol was added and the solution refluxed for 3 hours. The mixture was cooled and the tan precipitate was filtered off and dissolved in 100 ml. of water, filtered, and washed with ether-benzene. The pale yellow aqueous solution was then added to 50 ml. of cold \(\text{HN} \) hydrochloric acid. The white precipitate was filtered and dried to yield 2.9 g., m.p. 191-194\(^\circ\) of diacid. The ethylene glycol filtrate was diluted with 150 ml. of water and the solution
was filtered and washed with ether-benzene. Addition of the tan colored aqueous solution to 100 ml. of 4N hydrochloric acid yielded tan diacid (VI) which, on filtering and drying, weighed 5.8 g., m.p. 186-192°. The total yield was 97 per cent.

Several recrystallizations from glacial acetic acid yielded an analytical sample, m.p. 195-196°.

**Anal. (S)** Calculated for C_{19}H_{19}F_{6}O_{4}: C, 69.1; H, 5.8; F, 5.7

**Found:** C, 68.7; H, 6.1; F, 5.7

6a,12b-Dihydro-1-fluoro-12-methyl-
benzo(c)phenanthrene-5,8(6H,7H)-
dione (VII)

To 500 g. of polyphosphoric acid \(^{2,3,4}\) which was vigorously stirred at 165°, was added in 15 seconds, 25 g. of white

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(2) Generously supplied by Victor Chemical Company, Chicago, Illinois

(3) D. H. Phillips, Ph.D. Dissertation, The Ohio State University, 1958, p. 72-75


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3-(2-fluoro-2'-methylbenzhydryl)glutaric acid, m.p. 193-195°.
The mixture rapidly turned a dark brown. After 6 minutes, the hot mixture was poured into 1000 g. of ice and stirred well. The precipitate was extracted with ether-benzene leaving about 2 g. of insoluble material. The deep red organic layer was washed
Table 4

cyclization of 3-(2-fluoro-2-methylbenzydryl)glutaric acid to 6a,12b-dihydro-1-fluoro-12-methylbenzo-(c)phenanthrene-5,6(6h,7h)-dione (VII) with polyphosphoric acid

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<th>% Crys. Ketone</th>
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(a) The ratio of polyphosphoric acid to glutaric acid was 10:1 by weight.
with 10 per cent potassium carbonate solution, and treated in the usual manner. Crystallization of the red gum from benzene yielded 7.3 g. (32 per cent) of yellow crystalline diketone, m.p. 172-175° from the first crop, and 2.3 g. (10 per cent), m.p. 170-174° from the second crop. The infrared spectrum (potassium bromide wafer) in each case showed a band at 6.02 μ (s) and no band near 5.8 μ.

The dinitrophenylhydrazine derivative was prepared and recrystallized twice from nitrobenzene, m.p. over 300° with dec.

**Anal. (S)**

Calculated for C_{31}H_{23}N_6O_6F: C, 56.9; H, 3.5

Found: C, 56.8; H, 3.4

The potassium carbonate washings were acidified to yield 7.5 g. of a black solid. Recrystallization from benzene gave 5.5 g. of off-white crystals, m.p. 143-147°. Further recrystallization gave white keto-acid (XI), m.p. 147.5-149.0°, whose infrared spectrum (potassium bromide wafer) showed a broad band at 3.1 μ (s) (COOH) and bands at 5.87 μ (s) and 6.02 μ (s).

**Anal. (S)**

Calculated for C_{19}H_{17}O_3F: C, 73.1; H, 5.5

Found: C, 73.0; H, 5.2

**Cyclization with Anhydrous Hydrofluoric Acid**

Anhydrous hydrofluoric acid, 100 ml., was run into a 500 ml. polyethylene bottle containing 10 g. (.03 moles) of diacid, m.p. 191-194°. The diacid readily dissolved and a dark brown color appeared. The hydrofluoric acid was allowed to evaporate
over several days. The light-brown gum remaining was taken up with aqueous potassium carbonate and with ether-benzene. The layers were separated and the organic layer washed with base and treated in the usual manner to yield 0.1 g. of gold viscous oil which could not be crystallized. The infrared spectrum showed three bands in the 5.6-6.0 region.

The combined basic portions were added to 6N hydrochloric acid. The yellow gum which precipitated was taken up in ether-benzene and treated in the usual manner to yield 9.2 g. (97 per cent) of golden keto-acid (XI), m.p. 143-146°.

An attempt was made to prevent the rapid evaporation of the hydrogen fluoride by attachment of several feet of polyethylene tubing to the mouth of the flask. In this way very little evaporation of hydrogen fluoride occurred in 3 days. However, there was no change in product ratio.

When the reaction was run in a bomb at 60° for 3 hours, about 30 per cent of a neutral yellow oil was formed along with keto-acid. The yellow oil again could not be crystallized and its infrared spectrum showed broad bands in the 5.8-6.0 region.

Cyclization via the Keto-Acid Chloride

To a solution of 30 g. of thionyl chloride, in 50 ml. dry benzene at 65°, was added 6.0 g. (.019 moles) of keto-acid (XI), m.p. 146-148° in 50 ml. dry benzene. The solution bubbled and hydrochloric acid fumes escaped. After 1 hour a small sample was removed and its infrared spectrum showed sharp bands at 5.6 μ (s)
and 6.0 μ (s). The solvent was removed under vacuum and some tetrachloroethane was added and removed under vacuum. The tan gum was taken up in 100 ml. of tetrachloroethane and 5.64 g. (0.082 moles) of aluminum chloride was added at 30° with stirring. The mixture darkened and was held at 30° for 1 hour. It was then poured into 100 g. of ice and 1 N hydrochloric acid. Ether-benzene was added and the two layers were separated. The aqueous layer was washed with ether-benzene and the combined organic layers were washed with water and extracted with 10 per cent potassium carbonate solution. The organic layer was treated in the usual manner to yield 4.7 g. of neutral brown gum. Crystallization from ether afforded 2 g. (35 per cent) of yellow solid, m.p. 193-196° which showed a sharp band at 5.9 μ (s) in the infrared. Recrystallization gave white diketone (VII), m.p. 197-198.5°.

Anal. (G) Calculated for C_{19}H_{15}F_{2}O_{2}: C, 77.5; H, 5.1

Found: C, 77.3; H, 5.3

Addition of the carbonate solution yielded 0.85 g. of green solid, m.p. 125-140°. Recrystallization from benzene afforded 0.60 g. of off-white keto-acid (XI), m.p. 142-145°.

5,6,6a,7,8,12b-Hexahydro-1-fluoro-12-methylbenzo(c)phenanthrene-5,8-diol (VIII)

To a mixture of 1.5 g. of lithium aluminum hydride in 150 ml. of dry ether was added dropwise, with stirring, 4.7 g. (0.016 moles)
of diketone, m.p. 172-175°, in 90 ml. of dry benzene. An insoluble white precipitate formed immediately. After the addition was complete (10 minutes) the mixture was refluxed for 30 minutes. The excess hydride was decomposed by careful dropwise addition of water and the mixture was poured into a mixture of 100 ml. of 10 per cent sulfuric acid and ice. The two layers were separated and the aqueous layer extracted with ether-benzene. The combined organic layers were washed with water, 10 per cent potassium carbonate solution, and treated in the usual manner. The diol was allowed to precipitate from the incompletely removed solvent to yield 1.25 (89 per cent) of white solid, m.p. 159-183°, and .34 g. (7 per cent) of light yellow solid, m.p. 150-182°.

The dicarbethoxy derivative (XII) of the diol was prepared in the following manner: To a solution of 2 g. (.007 moles) of the diol, m.p. 159-183°, in 40 ml. of dry pyridine cooled in an ice bath, was added dropwise, with stirring, 6 ml. of ethyl chloroformate (Eastman White Label). During the addition the mixture went to a reddish color and a precipitate formed. The mixture was allowed to stand at room temperature for 5 hours and then refluxed for 1 hour. The cooled mixture was poured into 200 g. of ice and water. A yellow solid formed which, after standing in the refrigerator overnight, was filtered, dried, and recrystallized from ethanol to yield 1.48 g. (48 per cent) of off-white solid. Two recrystallizations from ethanol gave nice
white needles, m.p. 117-118°. The infrared spectrum (potassium bromide wafer) showed a sharp band at 5.8 μ (s) (C=O).

**Anal. (S)** Calculated for C_{25}H_{27}O_F: C, 67.9; H, 6.2; F, 1.3

Found: C, 67.5; H, 6.3; F, 1.3

1-Fluoro-12-methylbenzo(c)phenanthrene

A mixture of 1.25 g. (.016 moles) of the diol, m.p. 152-178°, 13 ml. xylene, and 18 mg. of iodine was heated to reflux temperature. Within a few minutes after refluxing started the iodine color disappeared and the diol had dissolved to give a light yellow solution. After 24 hours an additional 8 mg. of iodine was added. The iodine color again rapidly disappeared. After having refluxed a total of 100 hours, the yellow solution was cooled and diluted with ether-benzene, washed with sodium bisulfite solution and treated in the usual manner. The light-brown gum was dissolved in 7 ml. of chloroform and chromatographed on a 35x160 mm. column of activated alumina prewashed with benzene.

Two fractions were obtained:

1. 100 ml. of pale green benzene solution that fluoresced as light blue under ultraviolet light

2. 200 ml. of very pale yellow ethanol solution which, on evaporation, yielded .003 g. of yellow oil.

The first fraction was rechromatographed on a 35x150 mm. column of activated alumina prewashed with Skellysolve B to yield the following fractions:
(3) 300 ml. of colorless Skellysolve B solution which, on evaporation, yielded 1.27 g. of colorless oil having an ultraviolet maximum at 270 μm (ε = 2,000).

(4) 100 ml. of colorless Skellysolve B solution which, on evaporation, yielded 0.57 g. of colorless oil having ultraviolet maxima at 268 μm and 289 μm (ε = 17,600)

(5) 500 ml. of colorless Skellysolve B solution which, on evaporation, yielded 1.55 g. of colorless oil having an ultraviolet maximum at 289 μm (ε = 47,800).

(6) 200 ml. of ethanol solution which, on evaporation, yielded only traces of yellow oil.

Fraction 5 was crystallized with difficulty from oxygen-free absolute ethanol to yield 1.4 g. (39 per cent) of white crystals, m.p. 62-64°. Several recrystallizations from absolute ethanol gave white crystalline 1-fluoro-12-methylbenzo(c)phenanthrene, m.p. 66-67°.

Anal. (G) Calculated for C₉H₁₃F: C, 87.7; H, 5.0; F, 7.3
Found: C, 87.5; H, 5.0; F, 7.4

The 2,4,5,7-tetranitrofluorenone complex was prepared by mixing a hot solution of 0.15 g. of the 1-fluoro-12-methylbenzo-(c)phenanthrene in glacial acetic acid with 0.2 g. of 2,4,5,7-tetranitrofluorenone in hot glacial acetic acid and concentrating the solution to 5 ml. On cooling, 0.1 g. of dark wine-red
needles, m.p. 200-201° precipitated.

Anal. (G) Calculated for C_{32}H_{17}N_{4}O_F: C, 61.9; H, 2.7; F, 3.1; N, 9.0
Found: C, 61.8; H, 2.8; F, 3.1; N, 8.9

Resolution of 1-Fluoro-12-methylbenzo(c)phenanthrene

A solution of 2 g. (.008 moles) of the benzo(c)phenanthrene and 1.5 g. (.0034 moles) of (-)-2-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid in 15 ml. chloroform was prepared by refluxing for several minutes. The solution was evaporated down to about 10 ml. and allowed to stand at room temperature overnight. Filtration afforded 1.6 g. of red solid. The solid was taken up in ether-benzene and washed with dilute sodium bicarbonate solution. The organic layer was then treated in the usual manner to yield .63 g. of reddish oil. The oil was taken up in Skellysolve B-chloroform (80:20 by volume) and passed through a short column of activated alumina prewashed with Skellysolve B-chloroform (80:20). Evaporation yielded 0.58 g. of colorless oil \( [\alpha]_{D}^{21°} = -323° \) in chloroform (C=.016 g./ml.).

Rates of Racemization of 1-Fluoro-12-methylbenzo(c)phenanthrene

The rates were measured using the constant temperature bath shown in Figure 12. A liquid which had the desired boiling point (toluene, chlorobenzene, n-butanol-water) was brought to reflux in A. The system was allowed to reflux overnight to bring the glycerol bath (C) up to temperature. The sealed sample vials
Figure 12. - Constant temperature bath.

(A) Condenser
(B) Dry Ice condenser
(C) 500 ml. round-bottomed flask
(D) Refluxing liquid
(E) Glycerol bath
(F) Cork
(G) Thermometer
(see below) were rapidly introduced into the bath. After 15 to 30 minutes, the samples were removed at definite time intervals, cooled, and the rotations measured.

The samples for a typical run were prepared by weighing out .1570 g. of partially resolved compound \( [\alpha]^{25\circ}_D = -323\circ \) and dissolving this in 12 ml. of ortho-dichlorobenzene (the solvent used in all the runs—chosen simply for its high boiling point). The vials were filled with 1.2 ml. of solution each and then sealed. The sealed vials were weighed and reweighed after removal from the bath to insure that there was no solvent loss. The temperature remained within ± 0.1° during the course of the runs. From the results of the rotation readings, it is assumed that the readings are accurate to ±0.02°. The o-dichlorobenzene (Matheson, Coleman & Bell) had a boiling range of 179.5-180.5° and exhibited one peak on vapor phase chromatography.
SUMMARY

The synthesis of 1-fluoro-12-methylbenzo(c)phenanthrene in 8 steps, starting with o-fluorobenzaldehyde, is described. The complete resolution of this compound by means of the optically active complexing agent, (-)-α-(2,4,5,7-tetranitro-9-fluorenylideneaminoxy)propionic acid into the pure, optically active forms ([α]_D = ±580° ±15° in chloroform (c=0.005 g./ml.) has been achieved. The rates of racemization have been determined at 3 different temperatures and found to be:

k_91.7 = 1.27x10^{-6} \text{sec.}^{-1}, k_{109.7} = 9.48x10^{-6} \text{sec.}^{-1}, k_{130.6} = 78.2x10^{-6} \text{sec.}^{-1}.\] From these values, the activation energy was found to be 31.1 ± 0.2 kcal/mole, and the entropy of activation -2.08 ± 0.6 cal. deg.mole^{-1}.\]
AUTOBIOGRAPHY

I, Robert George Mentzer, was born in Toledo, Ohio, April 6, 1935. I received my secondary-school education in the public schools of Toledo, Ohio, and my undergraduate training at The University of Toledo, which granted me the Bachelor of Science degree in 1957. In September, 1958, I entered the Graduate School of The Ohio State University. During the time I was completing requirements for the Doctor of Philosophy degree, I received a National Science Foundation Cooperative Fellowship, and also held the positions of teaching assistant on the Freshman Chemistry staff, and Research Fellow.