CONTRIBUTION FROM THE ROLLIN H. STEVENS MEMORIAL LABORATORY OF THE DETROIT INSTITUTE OF CANCER RESEARCH]

The Structure of Inhoffen's Phenolic Steroids. II. The Synthesis of 1-Ethyl-2,8-dimethyl-5-methoxyphenanthrene and 1-Ethyl-2,8-dimethylphenanthrene[1]

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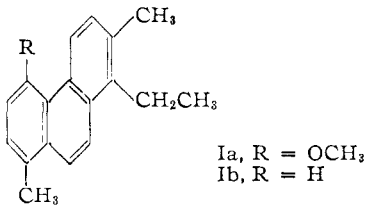
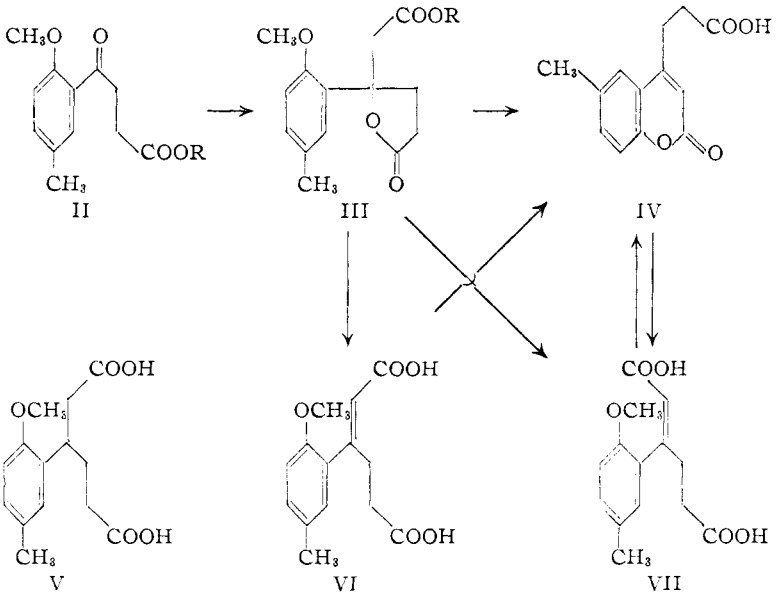
Synthetic approaches to 1-ethyl-2,8-dimethyl-5-methoxyphenanthrene (Ia) and to 1-ethyl-2,8-dimethylphenanthrene (Ib) have been developed. The synthetic samples were found to be identical with two of the dehydrogenation products from the methyl ether of Inhoffen's 17-keto-heterophenol.

In the previous paper,[2] the palladium-catalyzed dehydrogenation of one of Inhoffen's phenolic steroids was described. Two of the degradation products were said to have been identified as 1-ethyl-2,8-dimethyl-5-methoxyphenanthrene (Ia) and 1-ethyl-2,8-dimethylphenanthrene (Ib) by comparison with authentic samples, and it was therefore concluded that Inhoffen's phenolic steroids have a hydroxyl group in the 1-position and a methyl group at carbon-4. The synthesis of the two phenanthrene derivatives and the comparisons with the degradation products will be the subject of this paper.



Ia, R = OCH_3
Ib, R = H

A key intermediate in the synthesis of Ia was β-(6-methyl-4-coumarin)-propionic acid (IV), which was prepared in two ways. The Reformatsky reaction[3] with methyl β-(2-methoxy-5-methylbenzoyl)-propionate (II, R = CH_3) and methyl bromoactate yielded the methyl ester of the γ-lactone (III, R = CH_3). In contrast to the analogous cases,[4] this lactone ester was not converted to an unsaturated diacid by saponification but, instead, afforded the lactone acid (III, R = H). The conversion to unsaturated acids was accomplished, however, by the use of a stronger base. Treatment of the lactone acid (III, R = H) with sodium methoxide in hot methanol yielded an insoluble and a soluble sodium salt, corresponding to two unsaturated acids, m.p. 164–165° and 198–200°.[5] Both acids were isomeric with the lactone acid (III, R = H) but, unlike it, they were readily hydrogenated. The product of both reductions was the saturated diacid (V). That the two unsaturated acids represented the *cis* and *trans* isomers of β-(2-methoxy-5-methylphenyl)-$\Delta^{\alpha\beta}$ hexenedioic acid (VI and VII) was concluded from the ozonization which converted both isomers to β-(2-methoxy-5-methylbenzoyl)-propionic acid (II, R = H). The lactone acid (III, R = H) as well as both unsaturated acids (VI and VII) were transformed to β-(6-methyl-4-coumarin)-propionic acid (IV) by a hydriodic acid demethylation. However, only the unsaturated acid, m.p. 200°, was isolated (in addition to a large amount of unchanged starting material) when the coumarin derivative (IV) was heated with alkali and dimethyl sulfate. This may be considered as tentative evidence that the isomer of m.p. 200° has structure VII and that consequently structure VI applies to the isomer, m.p. 165°. Despite the fact that the ozonization indicates the unsaturated acids to be



(1) (a) This work was presented before the Division of Organic Chemistry at the 121st Meeting of the American Chemical Society in Milwaukee, Wis., April, 1952. (b) A part of this work was supported by a Research and Development Contract between the Detroit Institute of Cancer Research and the United States Atomic Energy Commission. Additional support was provided by institutional grants from the Michigan Cancer Foundation, the American Cancer Society, Inc., and The Kresge Foundation.

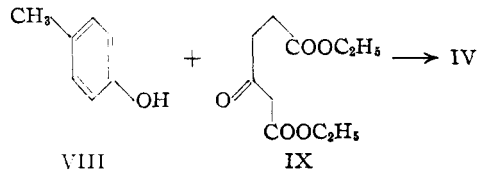
(2) A. S. Dreiding and A. Voltman, THIS JOURNAL, **76**, 537 (1954).

(3) The Reformatsky reaction with *o*-methoxyphenyl ketones as an approach to substituted coumarins has been studied by D. Chakravarti and B. Majumdar, *J. Ind. Chem. Soc.*, **15**, 136 (1938), and D. Chakravarti and N. Dutta, *ibid.*, **17**, 65 (1940).

(4) In two cases of a Reformatsky reaction with γ-keto esters, W. E. Bachmann and R. D. Morin, THIS JOURNAL, **66**, 553 (1944), and W. E. Bachmann and G. D. Johnson, *ibid.*, **71**, 3463 (1949), also found the γ-lactone esters to be the prime products. Saponification with dilute aqueous methanolic alkali converted both of these lactones to unsaturated acids.

(5) The resistance of system III to unsaturated acid formation was further shown by the fact that a small amount of III (R → H) was recovered even from the sodium methoxide treatment.

o-methoxycinnamic acid derivatives, they do not show the absorption characteristics in the ultraviolet which would be expected for such a conjugated system. In fact, the spectrum of the isomer, m.p. 200° (VII) in the 260–300 mμ region is almost identical with that of the saturated diacid (V) or of the lactone (III), and that of the isomer of m.p. 165° (VI) has a similar low intensity. This may be due to a steric interference which prevents coplanarity of the conjugated system.[6] Both unsaturated acids, however, show a higher absorption intensity at 215–220 mμ (α,β-unsaturated acid) than either the lactone or the saturated diacid.



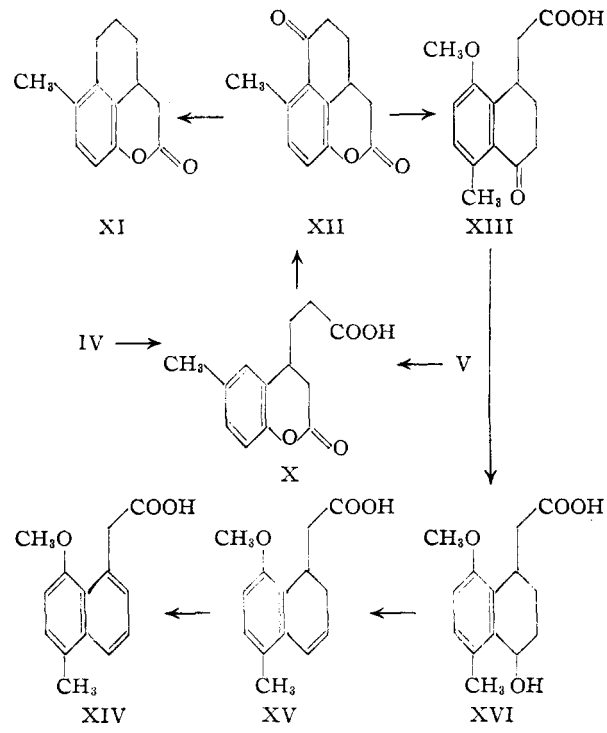
VIII IX

An alternative method of preparation for the coumarin derivative (IV) was available in the v. Pechmann synthesis.[7] The condensation of *p*-cresol (VIII) with diethyl β-ketoadipate (IX) in a 1:1 mixture of sulfuric and phosphoric acid afforded 11% of IV.

The 3,4-double bond in IV was resistant to catalytic hydrogenation, but when an alkaline solution of IV was treated with a nickel–aluminum alloy[8] a 57% yield of β-(6-methyl-3,4-dihydro-4-coumarin)-propionic acid (X) was obtained. The same dihydrocoumarin derivative X resulted from the demethylation of the saturated diacid V.

When a solution of X in a 3:2 mixture of phosphorus pentoxide and phosphoric acid was heated for two hours, the lactone of 4-keto-5-methyl-8-hydroxy-1,2,3,4-tetrahydro-1-naphthylacetic acid (XII) was obtained in 80% yield by merely pouring the solution into cold water. Demethylation, lactonization and cyclization took place all in one step, when the saturated diacid (V) was subjected to the same phosphorus pentoxide–phosphoric acid treatment, yielding 62% of the keto lactone (XII).[9]

The lactone ring in XII was opened with alkali and dimethyl sulfate to give the keto acid (XIII), which was reduced with sodium borohydride to the hydroxy acid (XVI). The latter was dehydrated in the crude form (possibly a mixture of stereoisomers) by the action of acetic anhydride and formic acid, and the resulting unsaturated acid XV, as its methyl ester, was subjected to a palladium-catalyzed dehydrogenation at 250°. Under these conditions a 44% yield of 8-methoxy-5-methyl-1-naphthylacetic acid (XIV) was obtained after saponification. There was some disproportionation at this temperature as indicated by the isolation of a small amount of 8-methoxy-5-methyl-1,2,3,4-tetrahydro-1-naphthylacetic acid, which could also be prepared by the Clemmensen reduction of XII, followed by the opening of the lactone ring in XI with sodium hydroxide and dimethyl sulfate. At 350°, the dehydrogenation of the methyl ester of XV appeared to be accompanied by some decarboxylation, for, in addition to a 49% yield of XIV, some neutral material was formed which may be 1,5-dimethyl-8-methoxynaphthalene. The best yield of XIV (68%) was obtained by conducting the catalytic dehydrogenation at 300°. The chemical dehydrogenation, with N-bromosuccinimide, resulted in a 36% yield of XIV.



XI XII XIII X XIV XV XVI

A lithium aluminum hydride reduction converted the methyl ester of XIV to β-(8-methoxy-5-methyl-1-naphthyl)-ethanol (XVIIa). Its mesylate was condensed with potassiomalonic ester and the product was methylated, saponified and decarboxylated to γ-(8-methoxy-5-methyl-1-naphthyl)-α-methylbutyric acid (XVIIIa).[10] The acid chloride of XVIIIa was cyclized with stannic chloride to 1-keto-2,8-dimethyl-5-methoxy-1,2,3,4-tetrahydrophenanthrene (XXa), which yielded 1-ethyl-2,8-dimethyl-5-methoxy-3,4-dihydrophenanthrene (XIXa) upon treatment with ethylmagnesium iodide. A mild palladium-catalyzed dehydrogenation afforded 1-ethyl-2,8-dimethyl-5-methoxyphenanthrene (Ia). The evidence for its identity with the degradation product reported in the preceding paper[2] consists of undepressed mixture melting points of the methoxyphenanthrenes themselves and of two derivatives.

(6) The presence of an *o*-methoxyl group may make this effect even stronger in this case than in a similar case observed by D. L. Turner, THIS JOURNAL, **73**, 3017 (1951). *Cf.* this article for further references.

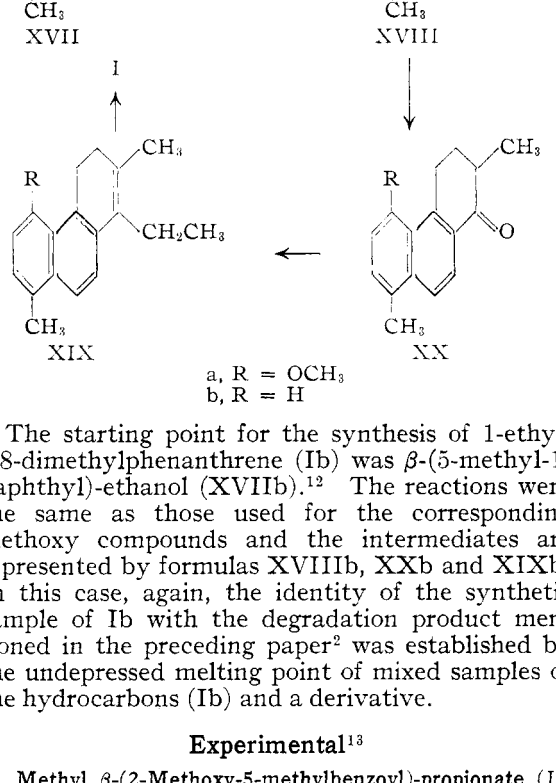
(7) H. v. Pechmann and C. Duisberg, *Ber.*, **16**, 2119 (1883).

(8) E. Schwenk, D. Papa, B. Whitman and H. F. Ginsberg, *J. Org. Chem.*, **9**, 175 (1944).

(9) The high yield of six-membered ring ketone formation in these cyclizations may be connected with the tendency of one of the carboxyl groups to form the six-membered lactone. This factor was not operative in a similar case studied by W. S. Johnson, A. R. Jones and W. P. Schneider, THIS JOURNAL, **72**, 2395 (1950), where apparently some five-membered ring ketone formation occurred.

(10) For a similar approach to the synthesis of related compounds see A. L. Wilds and L. W. Beck, THIS JOURNAL, **66**, 1688 (1944); A. L. Wilds and W. J. Close, *ibid.*, **69**, 3079 (1947); J. Herran, O. Mancera, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **16**, 899 (1951), and A. S Dreiding and W. J. Pummer, THIS JOURNAL, **75**, 3162 (1953).

The reactions described in the above paragraphs represent a novel and general approach to the synthesis of many alkyl-8-methoxy-1-naphthylacetic acids and consequently to many difficultly accessible alkyl-4-methoxyphenanthrenes. The method is general because the methyl *o*-methoxybenzoylpropionates, which are required as starting materials, can usually be made from the corresponding phenyl hydrogen succinates by a Fries reaction, followed by a methyl iodide–potassium carbonate methylation.[11]



The starting point for the synthesis of 1-ethyl-2,8-dimethylphenanthrene (Ib) was β-(5-methyl-1-naphthyl)-ethanol (XVIIb).[12] The reactions were the same as those used for the corresponding methoxy compounds and the intermediates are represented by formulas XVIIIb, XXb and XIXb. In this case, again, the identity of the synthetic sample of Ib with the degradation product mentioned in the preceding paper[2] was established by the undepressed melting point of mixed samples of the hydrocarbons (Ib) and a derivative.

Experimental[13]

Methyl β-(2-Methoxy-5-methylbenzoyl)-propionate (II, R = CH_3).—β-(2-Methoxy-5-methylbenzoyl)-propionic acid (II, R = H), m.p. 95–107° was prepared in 84% yield by the succinoylation of *p*-cresol methyl ether[14] in a 4:1 mixture of tetrachloroethane and nitrobenzene at 0° for 24 hours. A solution of 245 g. of II (R = H) in 800 cc. of methanol and 20 cc. of concentrated sulfuric acid was heated under reflux for 24 hours, cooled, diluted with 2 liters of iced water, saturated with salt, and extracted with five 100-cc. portions of ether. The organic extracts were washed with 500 cc. of 5% aqueous sodium hydroxide and saturated sodium chloride and dried. Concentration and cooling permitted 169 g. (65%) of **methyl β-(2-methoxy-5-methylbenzoyl)-propionate** to crystallize, m.p. 51–54°. An analytical sample, m.p. 53–54.5°, crystallized from petroleum ether as colorless needles; λ_{max}^{alc} 214, 248 and 315 mμ (ε 22,000, 8,230 and 3,860), λ_{min}^{alc} 233 and 273 mμ (ε 4,870 and 310).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.44; H, 6.83.

By acidification of the alkaline extracts, it was possible to isolate some β-(2-hydroxyl-5-methylbenzoyl)-propionic acid, m.p. 132–134° (reported[15] m.p. 135–136°).

A portion of the ester (II, R = CH_3) was saponified to give a pure sample of β-(2-methoxy-5-methylbenzoyl)-propionic acid (II, R = H) which crystallized from aqueous methanol and then ether–petroleum ether as colorless needles, m.p. 107–109° (reported[14,16] m.p. 115–117°).

Methyl Ester of the γ-Lactone of β-(2-Methoxy-5-methylphenyl)-β-hydroxyadipic Acid (III, R = CH_3).—To a stirred and heated mixture of 10 cc. of dry benzene, 10 cc. of dry ether, 4.775 g. of the keto ester (II, R = CH_3), and 5 g. of granulated zinc (20 mesh) was added 10 g. of methyl bromoacetate. After refluxing (exothermic reaction) for a half-hour, an additional 5 g. of zinc and 5 g. of bromoacetate was added and the mixture was heated for 1.5 hours. The complex was decomposed with cold dilute acetic acid and the organic solution was washed with several portions of 2% ammonium hydroxide and saturated sodium chloride. The residue, obtained by drying and concentrating the solution, was crystallized from ether–petroleum ether to give 4.49 g. (80%) of a slightly yellow solid, m.p. 48–55°. An analytical sample crystallized from the same solvents as clusters of colorless needles, m.p. 59–61°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.79; H, 6.65.

γ-Lactone of β-(2-Methoxy-5-methylphenyl)-β-hydroxyadipic Acid (III, R = H).—In another run of the same Reformatsky reaction with 10 g. of the keto ester (II, R = CH_3) the product was distilled through a short column, b.p. 170–181° (1 mm.), to give 11 g. of a thick amber oil, which was saponified by heating with 200 cc. of 10% aqueous sodium hydroxide for thirty-eight hours under an atmosphere of nitrogen. The basic solution was extracted with ether, acidified and the oily product taken up in ether. The addition of petroleum ether (b.p. 30–60°) and concentration yielded several crops of the **γ-lactone of β-(2-methoxy-5-methylphenyl)-β-hydroxyadipic acid** (III, R = H), m.p. 140–145°, yield 5.46 g. (49%). An analytical sample crystallized from acetone as large colorless prisms, m.p. 145–146.5°, λ_{max}^{alc} 224 and 277 mμ (ε 9,250 and 2,500), λ_{infl}^{alc} 284 mμ (ε 2,480), λ_{min}^{alc} 212 and 245 mμ (ε 7,700 and 500), neutral equivalent 260 (calcd. 264). The lactone acid in acetic acid does not absorb hydrogen in the presence of Adams catalyst at room temperature.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.11. Found: C, 63.77; H, 6.28.

The oily material in the mother liquor was treated with hydriodic acid in the manner described below to give 0.69 g. (7%) of **β-(6-methyl-4-coumarin)-propionic acid** (IV), m.p. 153–157° (see below).

In another experiment, the same Reformatsky reaction was conducted with 100 g. of II (R = CH_3) and the same proportions of reagents, except that benzene alone was used as the solvent, and that the distilled product was saponified by heating with 25% methanolic potassium hydroxide for two hours. By fractional crystallization it was possible to obtain 10.5 g. (9.4%) of ***trans*-β-(2-methoxy-5-methylphenyl)-$\Delta^{\alpha\beta}$-hexenedioic acid** (VII, see below), m.p. 170–190°, and 50 g. (44%) of the lactone acid (III, R = H), m.p. 130–140°.

***cis* and *trans* Isomers of β-(2-Methoxy-5-methylphenyl)-$\Delta^{\alpha\beta}$-hexenedioic Acid (VI and VII).**—A solution of 1 g. of the lactone acid (III, R = H) in methanolic sodium methoxide, prepared from 1 g. of sodium hydride and 50 cc. of methanol, was refluxed for 24 hours and concentrated to 15 cc. The insoluble sodium salt was filtered and acidified to give 0.28 g. (28%) of ***cis*-β-(2-methoxy-5-methylphenyl)-$\Delta^{\alpha\beta}$-hexenedioic acid** (VI), m.p. 157–161°. Recrystallization from ether formed colorless microprisms, m.p. 164–165° (above 210° a gas was evolved); λ_{max}^{alc} 218.5 mμ (ε 19,400), λ_{infl}^{alc} 260 and 289 mμ (ε 5,860 and 4,090).

(11) F. G. Baddar and L. S. El-Assal, *J. Chem. Soc.*, 3606 (1950).

(12) M. S. Newman and W. K. Cline, *J. Org. Chem.*, **16**, 934 (1951).

(13) The analyses are by Micro-Tech laboratories, Skokie, Illinois. The melting points are uncorrected. The ultraviolet absorption spectra were obtained through the courtesy of Dr. J. M. Vandenbelt of Parke, Davis and Co.

(14) K. W. Rosenmund and D. Shapiro, *Arch. Pharm.*, **272**, 313 (1934).

(15) R. B. Woodward and T. Singh, THIS JOURNAL, **72**, 494 (1950).

(16) The discrepancy between the found and the reported[14] melting point is not explainable at present.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.11. Found: C, 63.43; H, 6.24.

The methanolic mother liquor from the filtration of the sodium salt of VI was diluted with water and acidified to give 0.6 g. of solid, m.p. 136–172°. This was separated by fractional crystallization into 0.17 g. (17%) of recovered lactone acid (III, R = H), m.p. 144–146°, and 0.33 g. (33%) of *trans*-β-(**2-methoxy-5-methylphenyl**)-Δ$^{\alpha\beta}$-**hexenedioic acid** (**VII**), m.p. 197–199°. Recrystallization from ether gave colorless cubic prisms, m.p. 198–200° (slightly above the melting point a gas was evolved); λ_{max}^{alc} 285 mμ (ε 2,760), λ_{infl}^{alc} 219 mμ (ε 20,000), λ_{min}^{alc} 261 mμ (ε 2,150); neutral equivalent 137 (calcd. 132).

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.11. Found: C, 63.60; H, 6.24.

The ozonization of 120 mg. of VII, m.p. 198–200°, in 13 cc. of acetic acid and 7 cc. of ethyl acetate, followed by concentration, solution in 5% sodium hydroxide and acidification gave 32 mg. of β-(2-methoxy-5-methylbenzoyl)-propionic acid (II, R = H), m.p. 97–100°. Sublimation and crystallization from aqueous methanol raised the melting point to 105–107°, alone and when mixed with the sample prepared by the saponification of its ester (see above).

The application of the same ozonization procedure to 200 mg. of VI, m.p. 162–164°, resulted in 62 mg. of II, R = H, m.p. 103–105°, not depressed on admixture with the authentic sample.

β-(**2-Methoxy-5-methylphenyl**)-**adipic Acid** (**V**).—A solution of 2 g. of β-(2-methoxy-5-phenyl)-Δ$^{\alpha\beta}$-hexenedioic acid (VII), m.p. 195–197°, or VI, m.p. 162–164°, in 30 cc. of glacial acetic acid was stirred under an atmosphere of hydrogen in the presence of 0.1 g. of Adams catalyst. After 15 minutes, the uptake of hydrogen was quantitative and had stopped. Filtration, evaporation of the solvent and crystallization from ether–petroleum ether yielded 1.80 g. (89%) of β-(**2-methoxy-5-methylphenyl**)-**adipic acid** (**V**) as clusters of colorless microprisms, m.p. 135–136.5°, not raised on recrystallization from the same solvents, λ_{max}^{alc} 219.5 and 280.5 mμ (ε 8,650 and 2,660), λ_{infl}^{alc} 223.5 mμ (ε 8,590), λ_{min}^{alc} 214 and 250 mμ (ε 8,310 and 450).

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.15; H, 6.82. Found: C, 63.14; H, 7.06.

β-(**6-Methyl-4-coumarin**)-**propionic Acid** (**IV**). (**a**) **By the Demethylation of III, VI or VII.**—A solution of 6 g. of the γ-lactone of β-(2-methoxy-5-methylphenyl)-β-hydroxyadipic acid (III, R = H), m.p. 142–145°, in 25 cc. of 47% hydriodic acid and 15 cc. of glacial acetic acid was heated under reflux for two hours and filtered through Celite. The filtrate was poured into cold water to precipitate 3.8 g. (72%) of β-(**6-methyl-4-coumarin**)-**propionic acid** (**IV**) as a colorless solid, m.p. 158–160°. A portion crystallized from ether as colorless needles, m.p. 161–162.5°; λ_{max}^{alc} 216, 274 and 322 mμ (ε 24,150, 11,000, 5,610); λ_{min}^{alc} 209.5, 242 and 299 mμ (ε 20,900, 2,400, 3,700); neutral equivalent 233 (calcd. 232); on brief heating with 0.1 *N* sodium hydroxide, only one equivalent was neutralized. A solution of IV in acetic acid did not consume any hydrogen at atmospheric pressure with Adams catalyst.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.88; H, 5.21.

The same coumarin derivative (IV) resulted in approximately the same yield when either of the two unsaturated acids (VI or VII) was subjected to this hydriodic acid treatment.

(**b**) **By the von Pechmann Method.**—A solution of 2.16 g. of diethyl β-ketoadipate (IX) and 1.5 g. of *p*-cresol (VIII) in 20 cc. of 1:1 mixture of 85% phosphoric acid and concentrated sulfuric acid was allowed to stand at −25° for two hours and then at room temperature for 48 hours. Water was added and the steam volatile materials were removed by distillation. On cooling the residual aqueous solution, 250 mg. (11%) of β-(**6-methyl-4-coumarin**)-**propionic acid** (**IV**) crystallized as needles, m.p. 155–159° alone and when mixed with the sample prepared in the previous experiment.

Ring Opening of β-(**6-Methyl-4-coumarin**)-**propionic Acid** (**IV**).—A solution of 720 mg. of IV in 100 cc. of 10% aqueous sodium hydroxide was heated at reflux under an atmosphere of nitrogen for two hours, cooled, and treated with 15 cc. of dimethyl sulfate over a period of two hours with stirring. Acidification in the cold and saturation with sodium chloride precipitated 630 mg. of solid, m.p. 150–183°. Fractional crystallization yielded 265 mg. (32%) of *trans* β-(**2-methoxy-5-methylphenyl**)-Δ$^{\alpha\beta}$-**hexenedioic acid** (**VII**), m.p. 197–199, and 352 mg. (49%) of recovered coumarin derivative (IV), m.p. 155–159° alone and when mixed with the starting material. When mixed with the isomeric unsaturated acid (VI) the melting point was depressed to 130–134°.

β-(**6-Methyl-3,4-dihydro-4-coumarin**)-**propionic Acid** (**X**). (**a**) **From** β-(**6-Methyl-4-coumarin**)-**propionic Acid** (**IV**).—To a stirred solution of 40 g. of sodium hydroxide and 2 g. IV in 200 cc. of water was added 45 g. of Raney nickel alloy (50% nickel) in small portions over a period of one hour, when heat evolution and vigorous foaming took place. After further heating for four hours, cooling, and filtration through Celite, the clear colorless solution was acidified and extracted with chloroform. The extract was dried and concentrated and the residue crystallized from ether–petroleum ether to give 1.15 g. (57%) of β-(**6-methyl-3,4-dihydro-4-coumarin**)-**propionic acid** (X), m.p. 138–143°. The analytical sample obtained from the same solvents as colorless needles melted at 146–147°; λ_{max}^{alc} 227, 272 and 279.5 mμ (ε 7,460, 1,098 and 1,014), λ_{min}^{alc} 221, 257 and 277 mμ (ε 7,300, 713 and 946); neutral equivalent 235 (calcd. 234); saponification equivalent 119 (calcd. 117).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.80; H, 6.07.

(**b**) **From** β-(**2-Methoxy-5-methylphenyl**)-**adipic Acid** (**V**).—A solution of 10 g. of V, m.p. 135–136°, in 50 cc. of 57% hydriodic acid was heated under reflux for two hours and poured into cold water to give 6 g. (68%) of β-(**6-methyl-3,4-dihydro-4-coumarin**)-**propionic acid** (**X**), m.p. 140–142°. An additional 1.5 g. of X, m.p. 135–140°, was obtained by chloroform extraction, bringing the yield to 85%. Recrystallization from ether–petroleum ether raised the melting point to 146–147°.

Lactone of 4-Keto-5-methyl-8-hydroxy-1,2,3,4-tetrahydro-1-naphthylacetic Acid (**XII**).—This cyclization was patterned after the procedure of Gilmore and Horton.[17] A mixture of 120 g. of phosphorus pentoxide and 80 cc. of 85% phosphoric acid was homogenized by heating at 100° for two hours. After the addition of 10 g. of β-(6-methyl-3,4-dihydro-4-coumarin)-propionic acid (X), m.p. 142–144°, the mixture was heated at 100° for three hours with occasional swirling, cooled, and mixed with crushed ice. The precipitated **lactone of 4-keto-5-methyl-8-hydroxy-1,2,3,4-tetrahydro-1-naphthylacetic acid** (**XII**), m.p. 124–127°, weighed 7.38 g. (80%). A sample crystallized from dilute methanol as colorless needles, m.p. 128.5–130°; λ_{max}^{alc} 221.5, 248 and 306 mμ (ε 18,200, 10,600 and 2,830), λ_{min}^{alc} 242 and 274 mμ (ε 10,500 and 650).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.26; H, 5.86.

By applying the same procedure to 0.5 g. of β-(2-methoxy-5-methylphenyl)-adipic acid (V) there was obtained 0.255 g. (62%) of XII, m.p. 124–126° alone and when mixed with the sample prepared from X. The small acidic fraction which resulted from this experiment was not characterized.

When an attempt was made to cyclize β-(6-methyl-4-coumarin)-propionic acid (IV) by this procedure an almost quantitative recovery of starting material was observed.

Lactone of 5-Methyl-8-hydroxy-1,2,3,4-tetrahydro-1-naphthylacetic Acid (**XI**).—A mixture of 2 g. of XII, 20 cc. of toluene, 10 g. of amalgamated zinc, 25 cc. of concentrated hydrochloric acid and 10 cc. of water was heated under reflux for 24 hours. The toluene layer was separated, washed with water and concentrated to give 1.34 g. (71%) of the **lactone of 5-methyl-8-hydroxy-1,2,3,4-tetrahydro-1-naphthylacetic acid** (**XI**), m.p. 115–120°. A sample was recrystallized from petroleum ether in the form of colorless needles, m.p. 128–129°; λ_{max}^{alc} 270.5 mμ (ε 1,170), λ_{infl}^{alc} 220, 277 and 300 mμ (ε 7,060, 1,010 and 545), λ_{min}^{alc} 260 mμ (ε 1,000).

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.90; H, 7.35.

5-Methyl-8-methoxy-1,2,3,4-tetrahydro-1-naphthylacetic acid was prepared by the opening of the lactone ring in XI in an alkaline solution with excess dimethyl sulfate. Acidification and crystallization from petroleum ether gave an

(17) R. C. Gilmore, Jr., and W. J. Horton, THIS JOURNAL, **73**, 1411 (1951).

analytical sample as colorless needles, m.p. 159–160°; λ_{max}^{alc} 282.5 mμ (ε 2,050), λ_{infl}^{alc} 222, 275 and 300 mμ (ε 9,800, 1,940 and 420), λ_{min}^{alc} 250 mμ (ε 330).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.75. Found: C, 71.90; H, 7.85.

4-Keto-5-methyl-8-methoxy-1,2,3,4-tetrahydro-1-naphthylacetic Acid (XIII).—The solution resulting from the gradual addition, over a period of one hour, of 100 g. of dimethyl sulfate to a stirred solution of 10 g. of the lactone of 4-keto-5-methyl-8-hydroxy-1,2,3,4-tetrahydro-1-naphthylacetic acid (XII), m.p. 124–126°, in 50 cc. of methanol and 400 cc. of 10% aqueous sodium hydroxide was heated under reflux for one hour, cooled and filtered through Norite and Celite. The cold solution was acidified to give 9.55 g. (83%) of **4-keto-5-methyl-8-methoxy-1,2,3,4-tetrahydro-1-naphthylacetic acid (XIII)**, m.p. 145–147°. A sample crystallized from aqueous acetone as colorless plates, m.p. 155–156.5°; λ_{max}^{alc} 226, 256 and 325 mμ (ε 20,900, 8,100 and 3,600), λ_{min}^{alc} 243 and 283 mμ (ε 5,700 and 740). Compare this spectrum with that of 1-keto-5-methoxy-8-methyl-1,2,3,4-tetrahydronaphthalene, m.p. 35–37°,[18] λ_{max}^{alc} 226, 255 and 323 mμ (ε 22,230, 8,850 and 3,175), λ_{min}^{alc} 214, 243 and 280 mμ (ε 16,700, 6,460 and 760).

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.76; H, 6.49. Found: C, 67.81; H, 6.47.

4-Hydroxy-5-methyl-8-methoxy-1,2,3,4-tetrahydro-1-naphthylacetic Acid (XVI).—A solution of 10 g. of the keto acid (XIII) in a slight excess of aqueous sodium hydroxide (just basic to phenolphthalein) was treated with 3 g. of sodium borohydride, heated at 60–70° for one hour, cooled and acidified to give 9.0 g. (89%) of the **hydroxy acid (XVI)**, m.p. 160–172°. This sample may be a mixture of stereoisomers. Recrystallization from acetone afforded one isomer in pure form as long colorless prisms, m.p. 199–200°; λ_{max}^{alc} 285 mμ (ε 2,900), λ_{infl}^{alc} 220 and 279 mμ (ε 8,300 and 2,870), λ_{min}^{alc} 248 mμ (ε 575).

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.97; H, 7.51.

5-Methyl-8-methoxy-1,2-dihydro-1-naphthylacetic Acid (XV).—A solution of 4 g. of crude hydroxy acid (XVI), m.p. 160–172°, in 25 cc. of formic acid and 10 cc. of acetic anhydride was refluxed for three hours, cooled and diluted with 800 cc. of cold water to give 3.7 g. (99%) of the **unsaturated acid (XV)**, m.p. 128–132°. A sample crystallized from isopropyl ether as colorless needles, m.p. 137–138°; λ_{max}^{alc} 221.5, 268.5 and 305 mμ (ε 23,000, 9,500 and 2,660), λ_{infl}^{alc} 261 and 318 mμ (ε 8,250 and 1,970), λ_{min}^{alc} 245 and 294 mμ (ε 4,640 and 2,090). Compare this spectrum with that of 1-methyl-6,7-dehydroestrone,[19] which is very similar.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.11; H, 6.90.

5-Methyl-8-methoxy-1-naphthylacetic Acid (XIV).—A mixture of 0.8 g. of the methyl ester of XV (prepared from XV with diazomethane) and 0.8 g. of 5% palladium-on-charcoal was heated under an atmosphere of nitrogen at 230–240° for five minutes. The melt was extracted with hot acetone, the catalyst was filtered and the filtrate evaporated to dryness. Saponification of the residue in 20 cc. of hot 10% methanolic potassium hydroxide for one hour, evaporation of some of the methanol, dilution with water and filtration (Norite) gave a clear solution which on acidification precipitated 0.73 g. of a solid, m.p. 155–185°. Fractional crystallization from acetone and isopropyl ether afforded 0.33 g. (44%) of **5-methyl-8-methoxy-1-naphthylacetic acid (XIV)**, m.p. 197–201°. The melting point was raised to 203–205° by recrystallization from the same solvents, λ_{max}^{alc} 212.5, 238, 303, 315.5 and 329 mμ (ε 39,600, 30,800, 7,040, 5,560 and 3,820), λ_{min}^{alc} 230, 256, 313 and 326 mμ (ε 26,750, 800, 5,500 and 3,600).

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.05; H, 6.13. Found: C, 73.20; H, 6.18.

The material in the mother liquor consisted of **5-methyl-8-methoxy-1,2,3,4-tetrahydro-1-naphthylacetic acid,** which crystallized from petroleum ether, m.p. 157–159°, not depressed when mixed with the sample prepared from XI as described above.

When the dehydrogenation with 167 mg. of the methyl ester of XV was carried out in the same way, but at 300° for five minutes, and the saponification solution extracted with ether, there was formed 107 mg. (68%) of **5-methyl-8-methoxy-1-naphthylacetic acid (XIV)**, m.p. 180–190°, and only very little neutral material.

The dehydrogenation of 250 mg. of the methyl ester of XV at 350° for five minutes gave 115 mg. (49%) of XIV, m.p. 183–196°, and 53 mg. of a neutral oil. The latter formed an orange *sym*-**trinitrobenzene complex** from ethanol, m.p. 178–179°, which may be the derivative of **1,5-dimethyl-8-methoxynaphthalene.**

Anal. Calcd. for $C_{19}H_{17}N_3O_7$: C, 57.14; H, 4.29; N, 10.52. Found: C, 57.77; H, 4.42; N, 10.32.

The treatment of 246 mg. of the methyl ester of XV with 195 mg. of N-bromosuccinimide in 5 cc. of carbon tetrachloride, followed by saponification as above, produced 83 mg. (36%) of XIV, m.p. 192–196°, and a second crop of 30 mg. (13%) of lower melting material, m.p. 173–184°, which may contain some XV.

β-(5-Methyl-8-methoxy-1-naphthyl)-ethanol (XVIIa).—A mixture of 1 g. of lithium aluminum hydride, 1.5 g. of the oily methyl ester of XIV (prepared from XIV with diazomethane) and 150 cc. of dry ether was heated under reflux for one hour and the excess hydride was decomposed with 10 cc. of ethyl acetate and 10% aqueous hydrochloric acid. The ethereal layer was washed with dilute sodium hydroxide and water, dried and concentrated to give an oil which crystallized from isopropyl ether–cyclohexane at −25° as colorless needles, m.p. 65–66°, yield 1.12 g. (84%); λ_{max}^{alc} 216, 236, 302, 316 and 329.5 mμ (ε 40,300, 32,400, 7,650, 6,180 and 4,500), λ_{min}^{alc} 231, 256, 312.5 and 324 mμ (ε 30,650, 1,300, 5,830 and 3,130).

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.77; H, 7.45.

An amorphous **3,5-dinitrobenzoate**, m.p. 262–263°, precipitated as an orange solid from a colorless solution in dioxane and methanol.

Anal. Calcd. for $C_{21}H_{18}N_2O_7$: C, 61.46; H, 4.42; N, 6.83. Found: C, 61.45; H, 4.69; N, 7.07.

The methanesulfonate of XVIIa was formed when a solution of 0.8 g. of the alcohol (XVIIa) and 2 cc. of methanesulfonyl chloride in 10 cc. of anhydrous pyridine was allowed to stand at room temperature for 15 minutes and poured on crushed ice. Recrystallization from isopropyl ether yielded 0.93 g. (85%) as colorless plates, m.p. 79–80°.

Anal. Calcd. for $C_{15}H_{18}O_4S$: C, 61.20; H, 6.17; S, 10.89. Found: C, 61.50; H, 6.68; S, 10.86.

γ-(5-Methyl-8-methoxy-1-naphthyl)-α-methylbutyric Acid (XVIIIa).—A mixture of 2 g. of diethyl malonate, 0.035 g. of sodium hydride and 50 cc. of dry benzene was heated for one hour. The mesylate of XVIIa (0.5 g.) in 5 cc. of benzene was added and the mixture heated again with stirring for 12 hours. After the addition of another 0.035 g. of sodium hydride with heating for two hours, the mixture was treated with 10 cc. of methyl iodide, followed by heating for three hours. To the cooled mixture was added dilute hydrochloric acid and the residue from the benzene solution was saponified with 20% methanolic potassium hydroxide to give 0.19 g. (35%) of **γ-(5-methyl-8-methoxy-1-naphthyl-α-methyl-α-carboxybutyric acid,**[20] m.p. 180–185°. A sample was recrystallized from isopropyl ether and was obtained as cubic prisms, m.p. 197–198° with evolution of a gas.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.38; H, 6.60.

The methyl malonic acid derivative (36 mg.) was decarboxylated by heating at 200° for two minutes and the resulting **γ-(5-methyl-8-methoxy-1-naphthyl)-α-methylbutyric acid (XVIIIa)** was evaporatively distilled at 150–170° (0.1 mm.) and crystallized from petroleum ether to give 28 mg. (90%) of colorless needles, m.p. 95–96°.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.42; H, 7.48.

(18) J. Herran, O. Mancera, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **16**, 899 (1951).

(19) C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki and St. Kaufmann, THIS JOURNAL, **72**, 4540 (1950).

(20) In a forthcoming publication from this Laboratory an improved method for the condensation of the mesitylates of XXVIIa and XXVIIb with diethyl methylmalonate will be described.

1-Keto-2,8-dimethyl-5-methoxy-1,2,3,4-tetrahydrophenanthrene (XXa).—A solution of 76 mg. of the above butyric acid derivative (XVIIIa) in 5 cc. of benzene was heated with 3 cc. of oxalyl chloride for 20 minutes. The volatile components were removed at reduced pressure and the residual oily acid chloride in 5 cc. of benzene was treated at 0° with 1 cc. of anhydrous stannic chloride in 3 cc. of benzene. The red solution was allowed to stand for five minutes and poured into dilute hydrochloric acid. The neutral material was isolated as usual and crystallized from methanol to give 60 mg. (85%) of the **ketophenanthrene (XXa)**, m.p. 70–78°. Recrystallization from methanol raised the melting point to 85–87°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.14. Found: C, 80.02; H, 7.35.

The 2,4-dinitrophenylhydrazone of XXa crystallized from ethyl acetate–chloroform as orange-red micro-needles, m.p. 292–294° dec.

Anal. Calcd. for $C_{23}H_{22}N_4O_5$: C, 63.59; H, 5.11. Found: C, 64.13; H, 4.94.

1-Ethyl-2,8-dimethyl-5-methoxyphenanthrene (Ia).—To a solution of a Grignard reagent prepared from 1 g. of magnesium and 5 g. of ethyl iodide in 20 cc. of dry ether was added a crude oily sample of the ketophenanthrene (XXa) (prepared from 0.1 g. of the methylmalonic acid derivative as described in the previous experiment) in 5 cc. of dry ether. The yellow suspension was heated for one hour, treated with dilute acid and the organic layer was washed with base, dried and concentrated. The residue, presumably a crude sample of XIXa, was dehydrogenated by heating with 0.1 g. of 5% palladium-on-charcoal at 230–240° for five minutes. Extraction of the melt with benzene, filtration, concentration and crystallization from ethanol gave 0.025 g. (30% from the methylmalonic acid derivative) of **1-ethyl-2,8-dimethyl-5-methoxyphenanthrene (Ia)** as long brittle colorless needles, m.p. 64.5–65.5°; λ_{max}^{alc} 255, 281, 301, 314, 330, 346 and 362 mμ (ε 57,800, 31,800, 11,600, 14,300, 1,560, 2,230 and 2,440), λ_{min}^{alc} 234, 270, 297, 307, 326, 336 and 353 mμ (ε 19,600, 21,400, 11,900, 9,500, 1,060, 530, 530).

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.30; H, 7.82.

When this sample was mixed with an equal portion of the methoxyphenanthrene derivative (m.p. 64.5–65.5°) which had been obtained by the dehydrogenation of the methyl ether of one of Inhoffen's phenolic steroids,[2] the melting point was 64–65.5°.

The *sym*-trinitrobenzene complex crystallized from ethanol as orange needles, m.p. 198–198.7°. When mixed with this derivative of the steroidal degradation product (m.p. 196–197°) the melting point was 196.8–198°.

The picrate crystallized from ethanol as orange-red needles, m.p. 178–179°. The mixture with the picrate of the steroidal degradation product (m.p. 180.5–181.5°) melted at 179–180.2°.

β-(5-Methyl-1-naphthyl)-ethanol (XVIIb).—This alcohol was prepared by the procedure recently described by Newman and Cline,[12] but before their publication appeared. We are happy to confirm their observations. The ultraviolet absorption spectrum of the intermediate dehydrated Reformatsky acid, λ_{max}^{alc} 214.5, 219.5, 226 and 262 mμ (ε 21,200, 21,200, 15,100 and 9,270 mμ), λ_{min}^{alc} 217.5, 225 and 237 mμ (ε 20,600, 15,000 and 3,400), shows it to be 5-methyl-3,4-dihydro-1-naphthylacetic acid, as had been assumed by Newman and Cline.

The *p*-toluenesulfonate of XVIIb crystallized from ether–petroleum ether as colorless needles, m.p. 70.5–71.5°.

Anal. Calcd. for $C_{20}H_{20}O_3S$: C, 70.56; H, 5.92; S, 9.42. Found: C, 70.77; H, 6.28; S, 9.31.

The methanesulfonate of XVIIb was prepared in an 84% over-all yield from 5-methyl-1-naphthylacetic acid and crystallized from ether as colorless needles, m.p. 82–83°.

Anal. Calcd. for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10; S, 12.13. Found: C, 63.80; H, 6.17; S, 12.15.

γ-(5-Methyl-1-naphthyl)-α-methylbutyric Acid (XVIIIb).—This acid was prepared by the methods which had been developed for the corresponding 5-desmethyl compound by Bachmann, Gregg and Pratt[21] and by Wilds and Beck,[10] except that the *p*-toluenesulfonate of XVIIb was used instead of the bromide and methyl iodide instead of methyl bromide. The intermediate **γ-(5-methyl-1-naphthyl)-α-methyl-α-carboxybutyric acid** crystallized from isopropyl ether–petroleum ether as colorless prisms, m.p. 180–181° dec.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.30; H, 6.34. Found: C, 71.42; H, 6.50.

The γ-(5-methyl-1-naphthyl)-α-methylbutyric acid (XVIIIb), obtained in an over-all yield of 17%,[20] crystallized from ether petroleum ether as colorless needles, m.p. 128–130°.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49. Found: C, 79.23; H, 7.35.

1-Keto-2,8-dimethyl-1,2,3,4-tetrahydrophenanthrene (XXb).—The cyclization of 1.83 g. of XVIIIb by the method described by Wilds and Beck[10] gave 1.62 g. (95%) of the ketophenanthrene (XXb), m.p. 103–106° (reported[22] 108–109°).

1-Ethyl-2,8-dimethylphenanthrene (Ib).—The reaction between an ethyl Grignard reagent and 1.5 g. of the ketone (XXb) was performed as described above for XXa to give 1.5 g. (95%) of **1-ethyl-2,8-dimethyl-3,4-dihydrophenanthrene (XIXb)**, m.p. 98–104°. The analytical sample crystallized from ether–petroleum ether as colorless needles, m.p. 104–106°; λ_{max}^{alc} 259.5, 268 and 307 mμ (ε 41,500, 40,300 and 7,300), λ_{infl}^{alc} 284, 295 and 326 mμ (ε 4,860, 5,960 and 4,800), λ_{min}^{alc} 236 and 280 mμ (ε 13,000 and 4,500).

Anal. Calcd. for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.78; H, 8.40.

The dehydrogenation of 0.2 g. of XIXb as described for XIXa afforded 0.17 g. of **1-ethyl-2,8-dimethylphenanthrene (Ib)**, which on recrystallization from methanol–acetone was obtained as colorless plates, m.p. 115–116°; λ_{max}^{alc} 254, 262, 283, 294 and 306 mμ (ε 63,000, 83,000, 17,000, 17,400 and 22,000), λ_{infl}^{alc} 320–350 mμ (ε 300), λ_{min}^{alc} 234, 256, 279, 289 and 299 mμ (ε 10,000, 56,000, 15,000, 12,000 and 9,300).

Anal. Calcd. for $C_{18}H_{18}$: C, 92.25; H, 7.75. Found: C, 92.49; H, 7.69.

When this sample was mixed with the dehydrogenation product from the steroid[2] (m.p. 117–118°) it melted at 116–117°.

The *sym*-trinitrobenzene complex crystallized from benzene–methanol as yellow needles, m.p. 167–169°, which was unchanged when mixed with this derivative of the degradation product (m.p. 168–169°).

The 2,4,7-trinitrofluorenone complex crystallized from benzene–methanol as a dark orange solid, m.p. 173–175°.

Anal. Calcd. for $C_{31}H_{23}N_3O_7$: C, 67.75; H, 4.22; N, 7.64. Found: C, 67.79; H, 4.51; N, 7.92.

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