Summary

(1) The decrease of procaine in the aqueous parenteral solution containing 0.5% of procaine hydrochloride and 5% of glucose (PGI) was satisfactorily explained by opposing reactions between formation and hydrolysis of procaine-N-glucoside (PNG).

(2) The formation of PNG was proved to be an exothermic reaction, so that at epuilibrium state, higher the temperature, the less the amount of PNG formed, i.e. 66.5% of procaine was combined at 20° and 26.0% at 100°. The heat of reaction was found to be 4.77 Kcal.

(3) It was found that the activation energies of formation and hydrolysis of PNG were approximately 14.0 and 18.8 Kcal., respectively. There was a tendency that the velocity constant increases with time, which is considered to be caused by the decrease of pH.

(4) From the result obtained, it was concluded that storage of PGI in a refrigerator is not recommended and heat sterilization did not affect the amount of PNG at equilibrium.

(Rcceived December 1, 1956)

U.D.C. 547.677.6

15. Eiji Ochiai, Toshihiko Okamoto, and Mitsutaka Natsume: Syntheses of Alkylphenanthrenes. III.[1]

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In the preceding paper of this series,[1] we reported the syntheses of 1,6,7-substituted alkylphenanthrenes, in which 6 and 7 positions were asymmetrically substituted by methyl, ethyl, or isopropyl group. This paper treats the synthesis of a number of 1- and 6,7-*sym*-substituted alkylphenanthrenes and 1,8-dimethylphenanthrene by the same synthetic method.

One of these compounds, 1,8-dimethylphenanthrene was proved to be identical with a sample[2], obtained by the selenium dehydrogenation reaction of hypognavinol.

1, 8-Dimethyl- and 1-Methyl-8-ethylphenanthrenes

Two synthetic methods for 1,8-dimethyl- and 1-methyl-8-ethylphenanthrenes have already appeared in the literature.[3,4] We present a new, simpler route to these phenanthrenes.

β-(5-Methyl-1,2,3,4-tetrahydro-1-naphthyl)ethanol (II)[5], obtained from 5-methyltetralone-1, was converted to its chloride and reacted with diethyl malonate. After hydrolysis, decarboxylation, and dehydrogenation, γ-(5-methyl-1-naphthyl)butyric acid (III) was obtained which was cyclized to 1-oxo-8-methyl-1,2,3,4-tetrahydrophenanthrene (IV) as the available compound for the next Grignard reaction. Dehydrogenation was effected by heating with palladium-carbon.

The identification of the alkylphenanthrene (m.p. 187~191°) from the alkaloid with

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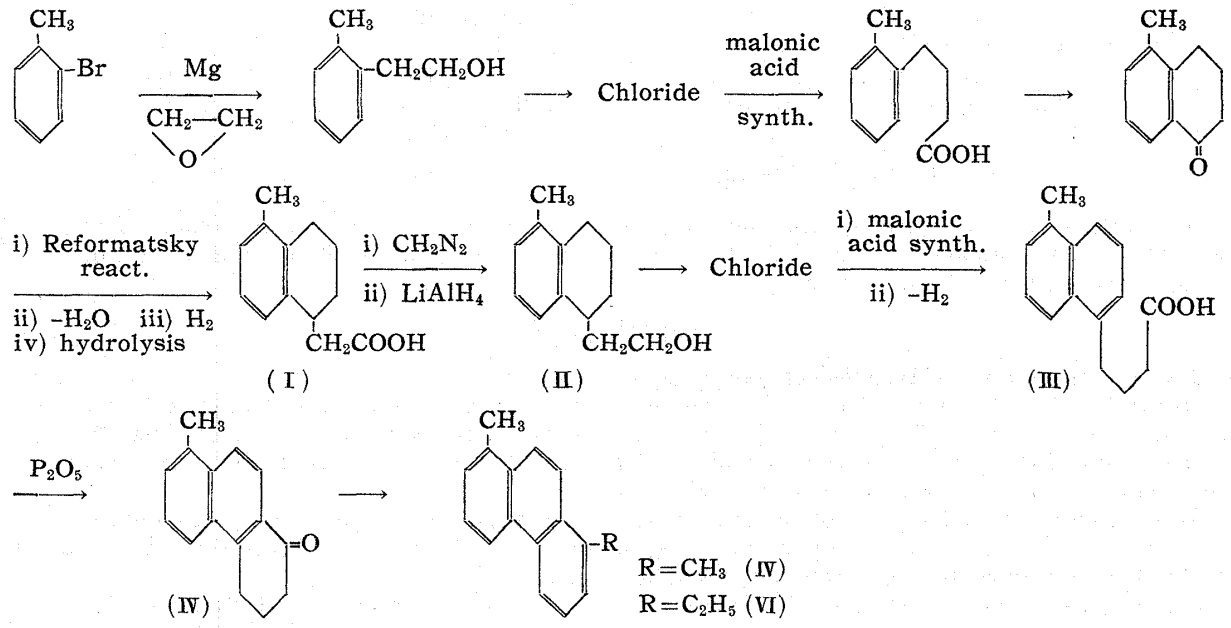
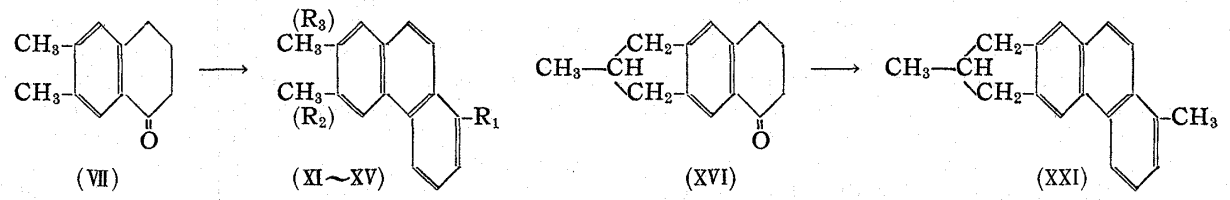
1) Part II: This Bulletin, **5**, 53(1957).
2) S. Sakai: J. Pharm. Soc. Japan, **76**, 1056(1956).
3) Haworth, Mavin, Sheldrick: J. Chem. Soc., **1945**, 454.
4) F.E. King, T.J. King: J. Chem. Soc., **1954**, 1373. cf. P.A. Robins, J. Walker: J. Chem. Soc., **1952**, 1610.
5) L. Ruzicka, K. Hofmann: Helv. Chim. Acta, **22**, 126(1932).

1,8-dimethylphenanthrene (V) was ascertained by mixed melting point examinations of their trinitrobenzene complex and free alkylphenanthrenes and further by the comparison of ultraviolet absorption spectra of the two samples.[2]

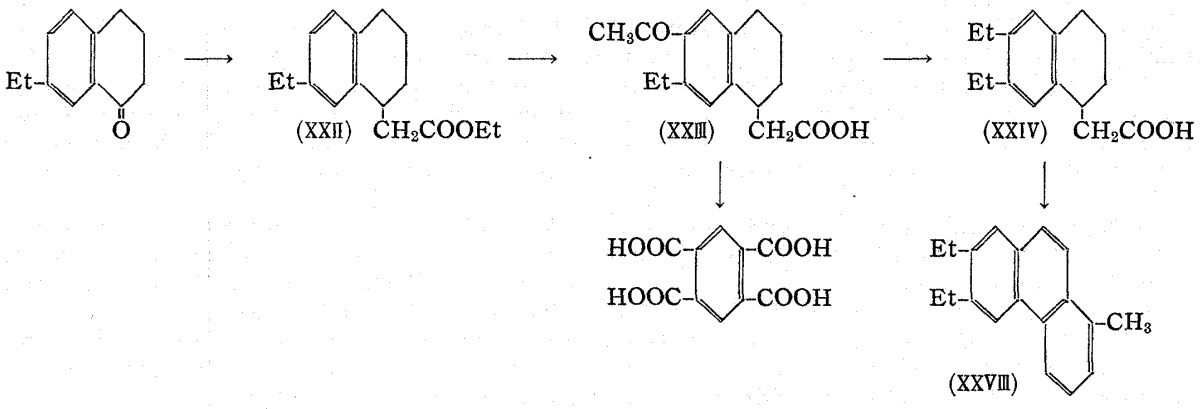


1,6,7-Substituted Alkylphenanthrenes

1-Alkyl-6,7-dimethyl- and 1-methyl-6,7-(2′-methylcyclopenteno)-phenanthrenes were synthesized through the same route as shown above.



The synthesis of 1-methyl-6,7-diethylphenanthrene needed an additional few steps. It has been shown[6] that the Friedel-Crafts acetylation of 2-ethyltetralin occurs in the neighboring 2-position. This phenomenon was also verified in the acetylation of ethyl 7-ethyl-1,2,3,4-tetrahydro-1-naphthylacetate by decomposing the acetylated compound to pyromellitic acid.



The properties of 1,6,7-alkylphenanthrenes thus obtained are shown in Table I.

6) M.C. Kloftzel, H.L. Herzog: J. Am. Chem. Soc., **72**, 1991(1950); K. Fleischer, F. Siefert: Ber., **53**, 1255(1920).

Table I.

	R_1	R_2	R_3	m.p.(°C)	Trinitrobenzene Complex m.p.(°C)	Picrate m.p. (°C)
(XI)	Me	Me	Me	125~125.5	182 ~183	165
(XII)	Et	Me	Me	89	165.5~166	—
(XIII)	*n*-Pr	Me	Me	97	155 ~155.5	—
(XIV)	*iso*-Pr	Me	Me	78	167 ~168	156
(XV)	*n*-Bu	Me	Me	83~84	145 ~145.5	—
(XXVIII)	Me	Et	Et	54	167 ~168	—
(XXI)	Me	CH_3-CH$\langle^{CH_2-}_{CH_2-}$		119~120	158 ~159	—

The microanalyses were carried out by the members of the Central Analysis Room of this Institute, by Mr. Yamaguchi, Kowa Co. Ltd., and also by Mr. Ieki of Shionogi & Co. Ltd., to all of whom the authors' thanks are due.

Experimental

[1] 1,8-Dimethyl- and 1-Methyl-8-ethylphenanthrenes

β-*o*-Tolylethanol[7]—From 80 g. of *o*-bromotoluene, 11.4 g. of Mg, and 40 g. of ethylene oxide, 42 g. of β-*o*-tolylethanol (b.$p_{16\sim18}$ 126~134°) was obtained with recovery of *o*-bromotoluene (25 g.).

β-*o*-Tolylethyl Chloride[7]—The chloride (32.5 g.)(b.p_7 106~110°) was prepared on treatment of the alcohol (42 g.) with dimethylaniline (75 g.) and $SOCl_2$ (74 g.).

γ-*o*-Tolylbutyric Acid—24 g. of malonic acid derivative, m.p. 139°(decomp.), was obtained from 32.5 g. of the above chloride as described by Wessely and Shiu Wang.[8] Decarboxylation of this dicarboxylic acid gave 16 g. γ-*o*-tolylbutyric acid (m.p. 59~60°).

5-Methyltetralone—Above acid (13 g.) was heated with polyphosphorous acid[9] (85% H_3PO_4 42 cc., P_2O_5 65 g.) on a steam bath for 1 hr. The resultant red brown liquid was poured into ice water. Precipitate was extracted with Et_2O, washed with Na_2CO_3 solution, and dried. Distillation *in vacuo* after the evaporation of Et_2O gave 9 g. of the tetralone, b.p_3 115~117°.

5-Methyl-1,2,3,4-tetrahydro-1-naphthylacetic Acid (I)—A mixture of 8 g. of the tetralone, 8 g. of Zn, 20 g. of Br-CH_2COOEt, and several pieces of I_2 in 40 cc. of benzene was heated on a steam bath for 5 hrs. The reaction mixture was poured into ice-cold dil. HCl. The benzene layer was separated, the aqueous layer was extracted with benzene, and the combined benzene solution was washed with dil. NH_4OH, dried over anhyd. Na_2SO_4, and evaporated. 50 cc. of Ac_2O was added to the residual oil, refluxed for 50 mins., and then poured into H_2O. Suspended oil was taken up in Et_2O and distilled under reduced pressure. 0.8 g. of coloress liquid (b.p_5 159~170°) was dissolved in EtOH (100 cc.) and hydrogenated employing Pd-C [carbon (1.0 g.), 1% $PdCl_2$(20 cc.)]. After removal of the catalyst and the solvent, the residue was heated in a solution of KOH (10 g.), MeOH (80 cc.), and H_2O (20 cc.) for 2 hrs. 6 g. of pure acetic acid derivative (m.p. 113~114°) was obtained by recrystallization from MeOH-H_2O. *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.72; H, 7.96.

Methyl 5-Methyl-1,2,3,4-tetrahydro-1-naphthylacetate—6 g. of the acid was esterified with CH_2N_2 in Et_2O, b.p_4 133~134°. Yield, 6 g.

β-(5-Methyl-1,2,3,4-tetrahydro-1-naphthyl)ethanol[5] **(II)**—The ester[6] was reduced to the alcohol with $LiAlH_4$ in Et_2O. Colorless oil. Yield, 5 g.

β-(5-Methyl-1,2,3,4-tetrahydro-1-naphthyl)ethyl Chloride—5 g. of the alcohol was chlorinated with 3.2 g. of φ-NMe_2 and 3.3 g. of SO_2Cl_2, and purified by distillation *in vacuo*, b.p_3 118°. Yield, 4.2 g.

γ-(5-Methyl-1-naphthyl)butyric Acid (III)—Above chloride (2.0 g.) was condensed with 3.8 g. of diethyl malonate in the presence of 0.4 g. of Na in 10 cc. of EtOH, decarboxylated and dehydrogenated over Pd-C. The reaction product was extracted with benzene and then taken up in Na_2CO_3 solution. The crystalline product (0.47 g.) separated out when alkaline solution was acidified. It showed m.p. 123~125°.

8-Methyl-1-oxo-1,2,3,4-tetrahydrophenanthrene (IV)—(III)(0.21 g.) was heated with polyphosphoric acid [85% H_3PO_4 (0.64 cc.) and P_2O_5 (1 g.)] on a steam bath for 1.5 hrs. The crude product was recrystallized from a mixture of petr. benzine and benzene to colorless pillars (100 mg.), m.p. 165~166°. *Anal.* Calcd. for $C_{15}H_{14}O$: C, 65.68; H, 6.71. Found: C, 65.38; H, 6.54.

1,8-Dimethylphenanthrene (V)—To the Grignard reagent [Mg (110 mg.), CH_3I (670 mg.), Et_2O (5 cc.)], a solution of the above ketone (100 mg.) in benzene (5 cc.) was added. After treating as usual, the resultant oil was boiled with AcOH (5 cc.) for 15 mins., diluted with H_2O, and extracted with Et_2O.

7) Nathar, McVey: J. Org. Chem., **4**, 464(1939).
8) F. v. Wessely, Shiu Wang: Ber., **73B**, 19(1940).
9) cf. H.R. Snyder, F.X. Weber: J. Am. Chem. Soc., **72**, 2965(1950).

The Et_2O solution was washed with H_2O aud Na_2CO_3 solution and dried over anhyd. Na_2SO_4. The evaporation of the solvent gave light brown oil, which was dehydrogenated over Pd-C at 280~290° for 1 hr. The product was extracted with benzene, washed with NaOH solution, dried over anhyd. Na_2SO_4, and concentrated. Recrystallization of the crude product from MeOH-benzene gave colorless plates (78 mg.), m.p. 189~191°. Trinitrobenzene complex, m.p. 170~172°. *Anal.* Calcd. for $C_{16}H_{14}\cdot C_6H_3O_6N_3$: C, 63.00; H, 4.09. Found: C, 63.89; H, 4.35.

1-Methyl-8-ethylphenanthrene (VI)—(IV)(100 mg.) was ethylated with EtMgBr. After AcOH treatment, it was dehydrogenated over Pd-C. Repeated recrystallization of the crude crystals from MeOH gave 29 mg. of (VI), m.p. 104~105°. Trinitrobenzene complex, m.p. 142~143°. *Anal.* Calcd. for $C_{17}H_{16}\cdot C_6H_3O_6N_3$: C, 63.73; H, 4.42. Found: C, 62.03; H, 4.25.

〔2〕 **1,6,7-Substituted Alkylphenanthrenes**

Ethyl 6,7-Dimethyl-1,2,3,4-terahydro-1-naphthylacetate (VII)—Reformatsky reaction was carried out in the usual way by heating 10 g. of 6,7-dimethyltetralone-1[10] with 18 g. of $BrCH_2COOEt$, 30 g. of Zn, and 0.7 g. of I_2 in a mixture of Et_2O (200 cc.) and benzene (200 cc.) for 6 hrs. After Ac_2O treatment followed by catalytic reduction, 12.3 g. of (VII), $b.p_5$ 163~165°(m.p. 123.5~124°), was obtained. *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.98; H, 8.08.

β-(6,7-Dimethyl-1,2,3,4-tetrahydro-1-naphthyl)ethanol(VIII)—6 g. of (VII) was reduced with $LiAlH_4$ (2 g.) in Et_2O; viscous liquid, $b.p_5$ 154°. Yield, 5.0 g.

Chloride of (VIII)—2.5 g. ($b.p_5$ 133~136°) of the chloride was produced by the chlorination of (VIII)(5.0 g.) with φ-NMe_2 (2.6 g.) and $SOCl_2$ (2.7 g.).

γ-(6,7-Dimethyl-1-naphthyl)butyric Acid (IX)—Above chloride (2.5 g.) was condensed with diethyl malonate, followed by the usual treatments. Recrystallized from petr. benzine to colorless pillars, m.p. 121~122°. Yield, 1.1 g. *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 80.23; H, H, 7.56.

1-Oxo-6,7-dimethyl-1,2,3,4-tetrahydrophenanthrene (X)—(IX)(0.3 g.) was cyclized in the usual way and recrystallized from MeOH to colorless plates (0.2 g.), m.p. 129~130°. *Anal.* Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 84.86; H, 6.84.

1,6,7-Trimethylphenanthrene (XI)—Grignard reaction in the syntheses of the following alkylphenanthrenes was carrid out employing 100 mg. of the ketones and 10 times the amount of required reagents, treated in the usual way, and dehydrogenated over Pd-C. (XI): Colorless pillars (from MeOH), m.p. 125~125.5°. Picrate: Orange needles (MeOH), m.p. 165°. *Anal.* Calcd. for $C_{17}H_{16}\cdot C_6H_3O_7N_3$: C, 61.47; H, 4.26. Found: C, 60.84; H, 3.81. Trinitrobenzene complex: Yellow needles (MeOH), m.p. 182~183°. *Anal.* Calcd. for $C_{17}H_{16}\cdot C_6H_3O_6N_3$: C, 63.73; H, 4.42. Found: C, 63.58; H, 4.03.

1-Ethyl-6,7-dimethylphenanthrene (XII)—Colorless plates (MeOH), m.p. 89°. Trinitrobenzene complex: Yellow needles (MeOH), m.p. 165.5~166°. *Anal.* Calcd. for $C_{18}H_{18}\cdot C_6H_3O_6N_3$: C, 64.42; H, 4.73. Found: C, 63.86; H, 4.66.

1-Propyl-6,7-dimethylphylphenanthrene (XIII)—Colorless crystals (MeOH), m.p. 97°. Trinitrobenzene complex: Yellow needles (MeOH), m.p. 155~155.5°. *Anal.* Calcd. for $C_{19}H_{20}\cdot C_6H_3O_6N_3$: C, 65.07; H, 5.02. Found: C, 65.07; H, 4.75.

1-Isopropyl-6,7-dimethylphenanthrene (XIV)—Colorless pillars (MeOH), m.p. 78°. Trinitrobenzene complex: Yellow needles (MeOH), m.p. 167~168°. *Anal.* Calcd. for $C_{19}H_{20}\cdot C_6H_3O_6N_3$: C, 65.07; H, 5.02; N, 9.11. Found: C, 62.96; H, 4.79; N, 9.40. Picrate: Orange needles, m.p. 156°.

1-Butyl-6,7-dimethylphenanthrene (XV)—Colorless crystals (MeOH), m.p. 83~84°. Trinitrobenzene complex: Yellow needles (MeOH), m.p. 145~145.5°. *Anal.* Calcd. for $C_{20}H_{22}\cdot C_6H_3O_6N_3$: C, 65.67; H, 5.30. Found: C, 63.46; H, 5.22.

1-Methyl-6,7-(2′-methylcyclopentano)phenanthrene

β-(2-Methyl-1-indanyl)propionic Acid[11]—2-Methylindane (24.5 g.) was reacted with succinic anhydride (20 g.) by use of $AlCl_3$ (50 g.) in $Cl_2CHCHCl_2$ (65 cc.). 30 g. of the product, m.p. 102~103° (from Et_2O-benzene), was obtained. The purest sample showed m.p. 104°. *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 71.72; H, 6.88.

γ-(2-Methyl-1-indanyl)bytyric Acid[11]—Above acid (29 g.) was reduced by the Clemmensen method. Yield, 22 g.

6,7-(2′-Methylcyclopentano)tetralone-1 (XVI)—The acid (20 g.) was cyclized in the usual way and purified by distillation *in vacuo*, $b.p_6$ 165~166°, m.p. 45~46°. Yield, 15 g.

Ethyl 6,7-(2′-Methylcyclopentano)-1,2,3,4-tetrahydro-1-naphthaleneacetate (XVII)—Reformatsky reaction was carried out employing 9 g. of the tetralone, 6 g. of Zn, and 15 g. of $BrCH_2COOEt$, the usual treatments and catalytic reduction followed. Purified by distillation *in vacuo*, $b.p_3$ 170~173°. Yield, 9.8 g. The ester was hydrolysed to the acid, m.p. 136~137°. *Anal.* Calcd. for $C_{16}H_{20}O_2$ (Acid): C, 78.65; H, 8.25. Found: C, 78.10; H, 8.10.

10) E. de Barry Barnett, F. G. Sanders: J. Chem. Soc., **1933**, 434.
11) Prepared after the method of Barnett and Sanders.

β-[6,7-(2'-Methylcyclopentano)-1,2,3,4-tetrahydro-1-naphthyl]ethanol (XVIII)—(XVII) was reduced with $LiAlH_4$ to viscous liquid, $b.p_5$ 185°.

Chloride of (XVIII)—The chloride (4.3 g.)($b.p_3$ 147~151°) was obtained from the alcohol (7 g.), φ-NMe_2 (5.5 g.), and $SOCl_2$ (5.4 g.).

γ-[6,7-(2'-Methylcyclopentano)-1-naphthyl]butyric Acid (XIX)—The chloride (4.3 g.) was condensed with diethyl malonate in the usual way, hydrolysed, decarboxylated, and dehydrogenated. Yield, 1.2 g. (m.p. 146~149°).

6,7-(2'-Methylcyclopentano)-1-oxo-1,2,3,4-tetrahydrophenanthrene (XX)—Above acid (0.5 g.) was cyclized in the usual way, m.p. 130~131°. Yield, 0.1 g. *Anal.* Calcd. for $C_{18}H_{16}O$: C, 86.36; H, 7.25. Found: C, 86.49; H, 7.17.

1-Methyl-6,7-(2'-methylcyclopentano)phenanthrene (XXI)—The ketone was methylated and dehydrogenated over Pd-C. Colorless plates (MeOH), m.p. 119~120°. Trinitrobenzene complex: Yellow needles (MeOH), m.p. 158~159°. *Anal.* Calcd. for $C_{19}H_{18}\cdot C_6H_3O_6N_3$: C 65.35; H,4.61. Found: C, 65.26; H, 4.35.

1-Methyl-6,7-diethylphenanthrene

6-Acetyl-7-ethyl-1,2,3,4-tetrahydro-1-naphthaleneacetic Acid (XXIII)—Ethyl 7-ethyl-1,2,3,4-tetrahydro-1-naphthylacetate (XXII)[12](40 g.) was acetylated employing 20 g. of AcCl, 15 g. of $AlCl_3$, and 180 cc. of $Cl_2CHCHCl_2$, $b.p_{0.06}$ 169~185°. Yield, 28 g. The acetate (28 g.) was hydrolysed to (XXIII), m.p. 126~127°. Yield. 9 g. *Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.25; H, 7.62.

6,7-Diethyl-1,2,3,4-tetrahydro-1-naphthylacetic Acid (XXIV)—The usual Clemmensen reduction of (XXIII)(9 g.) afforded 7.9 g. of (XXIV), m.p. 67~70°. 7.5 g. of the Me ester of (XXIV) was obtained by methylation with CH_2N_2, $b.p_3$ 151~155°.

β-(6,7-Diethyl-1,2,3,4-tetrahydro-1-naphthyl)ethanol (XXV)—The ester of (XXIV)(7.5 g.) was reduced with $LiAlH_4$. $b.p_5$ 170~171°. Yield, 6.5 g.

Chloride of (XXV)—2.5 g. of the chloride ($b.p_5$ 150~151°) was obtained from (XXV)(6.5 g.), φ-NMe_2 (5.1 g.), and $SOCl_2$ (5.0 g.).

γ-(6,7-Diethyl-1-naphthyl)butyric Acid (XXVI)—Above chloride (2.5 g.) was condensed with diethyl malonate, hydrolysed, decarboxylated, and dehydrogenated, m.p. 107~108°. Yield, 1.3 g. *Anal.* Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.75; H, 8.88.

1-Oxo-6,7-diethyl-1,2,3,4-tetrahydro-1-phenanthrene (XXVII)—(XXVI)(1.3 g.) was cyclized in the usual way, m.p. 81~82°. Yield, 0.5 g. *Anal.* Calcd. for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.35; H, 8.00.

1-Methyl-6,7-diethylphenanthrene (XXVIII)—The ketone was methylated and dehydrogenated over Pd-C; colorless crystals (MeOH), m.p. 54°. Trinitrobenzene complex: Yellow needles (MeOH), m.p. 167~168°. *Anal.* Calcd. for $C_{19}H_{20}\cdot C_6H_3O_6N_3$: C, 65.07; H, 5.02. Found: C, 65.80; H, 4.91.

Oxidative Degradation of (XXIII)—A solution of 0.3 g. of (XXIII) in 9 cc. of HNO_3 (d=1.40) was refluxed for 5 hrs. After the addition of 2 cc. of HNO_3 (d=1.40), the solution was condensed to 2 cc. within 2 hrs. The precipitate was separated from the liquid by decantation, diluted with acetone, and methylated with CH_2N_2 in Et_2O. After the solvents were evaporated, the residue was diluted with benzene and purified by alumina chromatography, m.p. 141~142°. This sample was identified with tetramethyl pyromellitate by admixture.

Oxidative Degradation of (XVII)—0.1 g. of (XVII) was oxidized with HNO_3 (d=1.40) and gave a sample, m.p. 138~141°, which was identified with tetramethyl pyromellitate by admixture.

Summary

Seven alkylphenanthrenes of 1,8-dialkyl and 1,6,7-trialkyl substituted were synthesized. One of these, 1,8-dimethylphenanthrene, was identical with an alkylphenanthrene derived from hypognavinol, an aconite alkaloid.

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12) Part I. E. Ochiai, *et al.*: This Bulletin, **5**, 48 (1957).