UDC 547.677.5.07

121. **Hideaki Shirai and Noriichi Oda**: Studies on Phenanthrene Derivatives. III.1) Synthesis of 2-Methoxy-5,6-methylenedioxyphenanthrene and 2-Methoxy-6,7-methylenedioxyphenanthrene.

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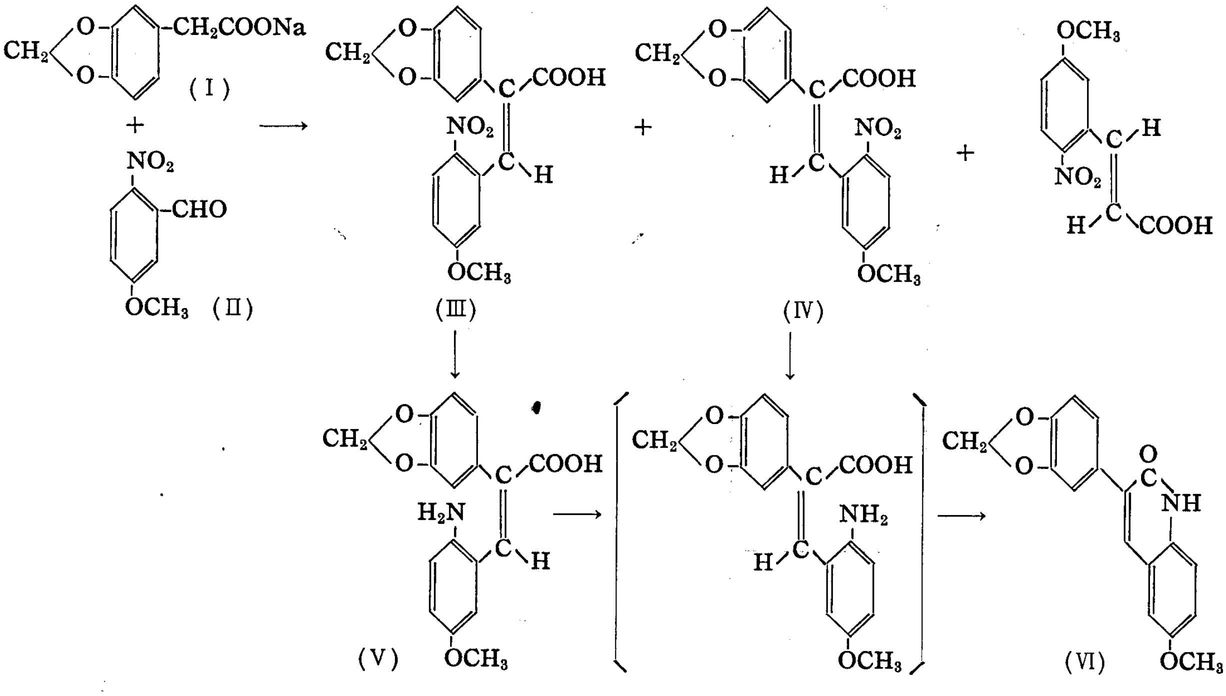
In the preceding papers of this series,1,2) the authors reported on the syntheses of some phenanthrene derivatives related to aporphine alkaloids. In the present paper, the synthesis of 2-methoxy-5,6-methylenedioxy- and 2-methoxy-6,7-methylenedioxy-phenanthrenes is described in detail.

Condensation of sodium homopiperonylate (I) with 2-nitro-5-methoxybenzaldehyde3) (II) gave a mixture of stereoisomers consisting chiefly of the required *trans*-α-(3,4-methylenedioxyphenyl)-2-nitro-5-methoxycinnamic acid (III), together with a small amount of the *cis* isomer (IV) and a trace of *trans*-2-nitro-5-methoxycinnamic acid as a by-product. Separation of the isomers was accomplished by repeated recrystallizations of the crude reaction product from ethanol, in which the *cis* isomer was comparatively soluble than the *trans* isomer. On reduction with ferrous sulfate, the *trans*-acid (III) gave the corresponding aminocinnamic acid (V), while the *cis*-acid (IV) gave the corresponding carbostyril (VI), because the intermolecular condensation will take place more easily when the carboxyl group is near the amino group.



The *trans*-aminocinnamic acid (V) was then submitted to the Pschorr reaction in methanolic solution, but the product obtained was not the desired phenanthrenecarboxylic acid, but an unexpected amino acid. The structure of this compound was examined and was proved to be 2,2′-hydrazo-bis[α-(3,4-methylenedioxyphenyl)-5-methoxycinnamic acid]

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1) Part II : Yakugaku Zasshi, **79**, 245(1959).

2) H. Shirai, N. Oda : *Ibid.*, **79**, 241(1959).

3) This Bulletin, **8**, 744(1960).

(VII) from the results of microanalysis, ultraviolet and infrared spectra, and also from the fact that on catalytic hydrogenation over palladium-carbon, (VII) absorbed three moles of hydrogen to give dihydrocarbostyril derivative (VIII), which was identical with a specimen prepared from *trans*-nitrocinnamic acid (III) by the same hydrogenation. The ultraviolet spectrum of the bis-compound (VII) in its ethanolic solution is very similar to that of *trans*-aminocinnamic acid (V) and of carbostyril (VI) as shown in Fig. 1.

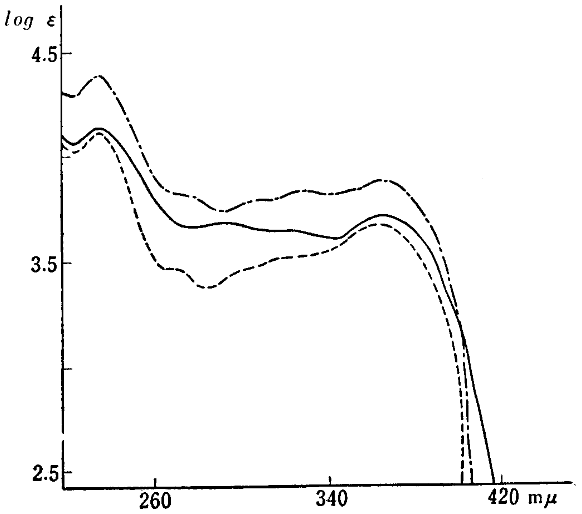
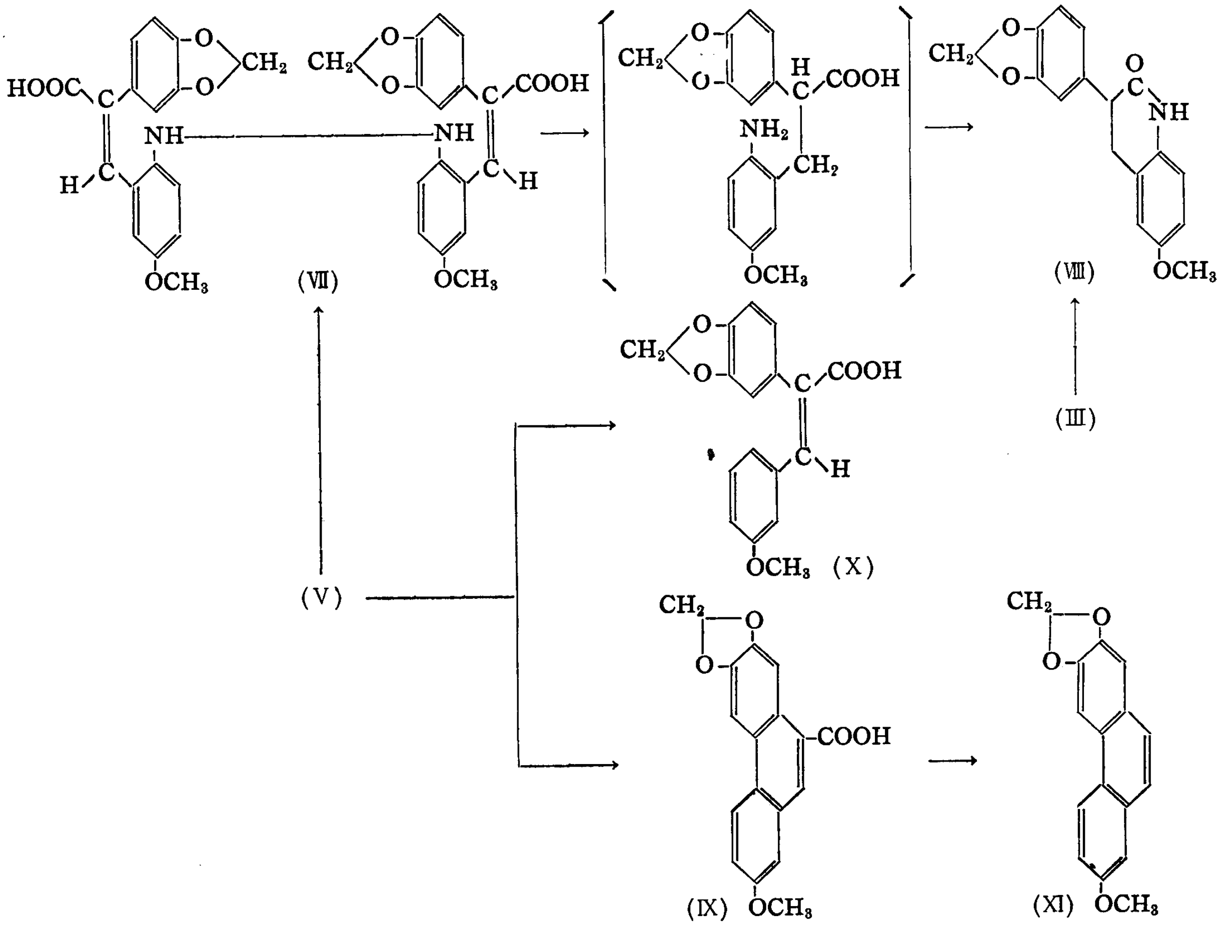


Fig. 1. Ultraviolet Absorption Spectra (in EtOH)

——— *trans*-α-(3,4-Methylenedioxyphenyl)-2-amino-5-methoxycinnamic acid

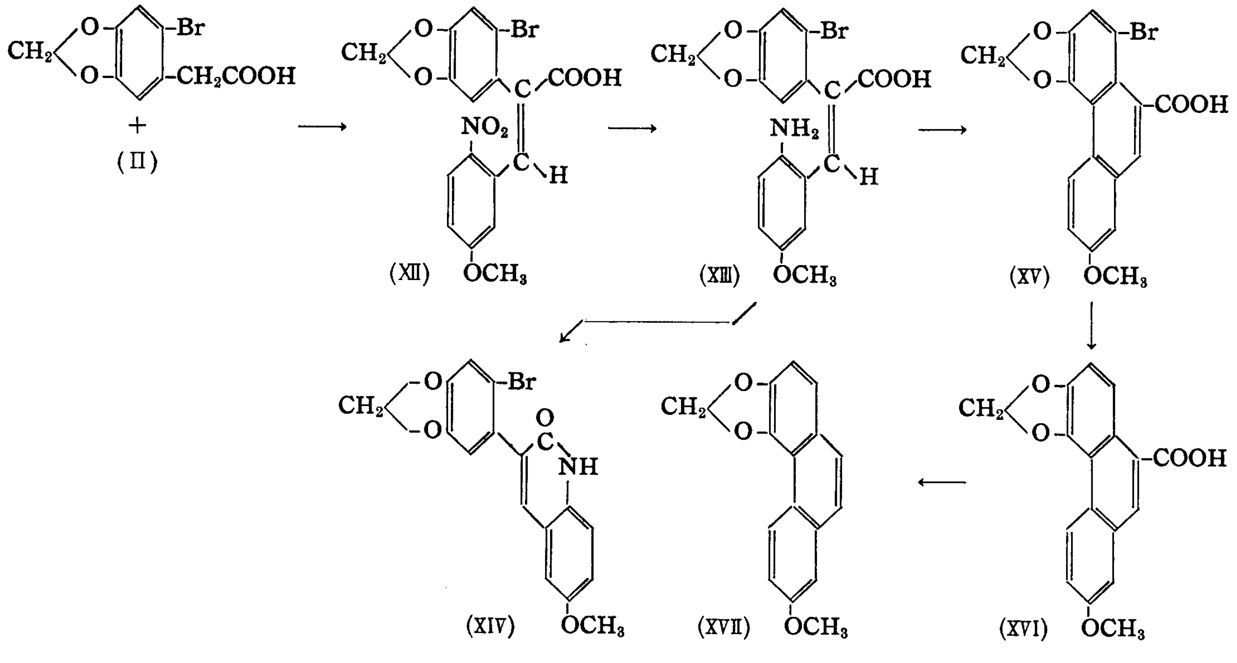
········· 3-(3,4-Methylenedioxyphenyl)-6-methoxycarbostyril

– – – – 2,2′-Hydrazo-bis[α-(3,4-methylenedioxyphenyl)-5-methoxycinnamic acid]



The alternate method to the desired cyclized compound was accomplished when the aminocinnamic acid (V) was treated in ethanolic solution containing a small amount of sodium hypophosphite. By this reaction, two acidic materials, (IX) and (X), were obtained. The former (IX) was confirmed to be phenanthrene derivate by its ultraviolet spectrum and the latter (X) was proved to be *α*-(3,4-methylenedioxyphenyl)-3-methoxycinnamic acid by its melting point and mixed melting point determination with authentic specimen prepared by the method of Kostanecki, *et al.*4) Similar side reaction was investigated by the senior author5) and a deaminated cinnamic acid was obtained in analogous synthesis of phenanthrene possessing 3,4-dimethoxy group. The decarboxylation of the acid (IX) was achieved by boiling with copper powder in quinoline, yielding the corresponding phenanthrene (XI). According to microanalysis, ultraviolet spectrum, and the synthetic pathway, it was determined that this phenanthrene is a methoxymethylenedioxyphenanthrene, but it has not been established whether the substance is 2-methoxy-5,6-methylenedioxyphenanthrene or 2-methoxy-6,7-methylenedioxyphenanthrene.

Therefore, in addition to proving the location of the methylenedioxy group, a synthesis of 2-methoxy-5,6-methylenendioxyphenanthrene (XVII) was carried out. Condensation of (II) with sodium 6-bromohomopiperonylate by means of the Perkin-Oglialoro reaction gave *trans*-*α*-(2-bromo-4,5-methylenedioxyphenyl)-2-nitro-5-methoxycinnamic acid (XII) and a trace of *trans*-2-nitro-5-methoxycinnamic acid, but no *cis*-isomer of (XII) was obtained. *trans*-Bromocinnamic acid (XII) was reduced with ferrous sulfate to the corresponding aminocinnamic acid (XIII), which was then diazotized with sodium nitrite. Decomposition of the diazonium salt with copper powder gave bromo-phenanthrenecarboxylic acid (XV), which was dehalogenated and finally decarboxylated to 2-methoxy-5,6-methylenedioxyphenanthrene (XVII). It now has been found that the afore-mentioned phenanthrene (XI) is quite different from this phenanthrene (XVII) and, accordingly the structure of (XI) must be 2-methoxy-6,7-methylenedioxyphenanthrene.



Experimental[*2]

***cis*- and *trans*-*α*-(3,4-Methylenedioxyphenyl)-2-nitro-5-methoxycinnamic Acid (III and IV)**—A mixture of 6 g. of sodium homopiperonylate (I), 5.4 g. of 2-nitro-5-methoxybenzaldehyde (II), and 30 cc. of Ac_2O was heated at 110° for 7 hr. After addition of 60 cc. of water and warming to decompose Ac_2O, the resulting mixture was evaporated *in vacuo* and the residue was extracted with 500 cc. of

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[*2] All m.p.s are uncorrected.

4) S. V. Kostanecki, J. Sulser : Ber., **38**, 941(1905).

5) H. Shirai : Yakugaku Zasshi, **63**, 517(1943).

5% NH_4OH. The basic solution was washed with Et_2O. After acidification of the solution with conc. HCl the resulting acid material was recrystallized from EtOH to give *trans*-α-(3,4-methylenedioxyphenyl)-2-nitro-5-methoxycinnamic acid (III) as yellow prisms, m.p. 175°. Yield, 4.1 g. *Anal.* Calcd. for $C_{17}H_{13}O_7N$: C, 59.48; H, 3.82; N, 4.08. Found : C, 59.50; H, 4.14; N, 4.20. UV $\lambda_{\max}^{\mathrm{EtOH}}$ 298 mμ (log ε 4.08).

On concentration of the mother liquor, the *cis*-isomer was obtained as yellow needles, m.p. 188~189°. Yield, 0.03 g. *Anal.* Calcd. for $C_{17}H_{13}O_7N$: C, 59.48; H, 3.82; N, 4.08. Found : C, 59.32; H, 3.79; N, 4.10. UV: $\lambda_{\max}^{\mathrm{EtOH}}$ 302 mμ (log ε 4.20).

A trace of *trans*-2-nitro-5-methoxycinnamic acid was also obtained from the mother liquor as colorless needles, m.p. 229°.[6]

***trans*-α-(3,4-Methylenedioxyphenyl)-2-amino-5-methoxycinnamic Acid (V)**—A solution of 1.4 g. of *trans*-nitrocinnamic acid (III) in 28 cc. of 5% NH_4OH was added gradually into a mixture of 7 g. of $FeSO_4 \cdot 7H_2O$ in 14 cc. of water and 17 cc. of 28% NH_4OH under continuous stirring. After addition, the mixture was heated on a water bath for 20 min. and then filtered. The filtrate and the washings from $Fe(OH)_3$ were combined and acidified with conc. HCl to pH 5.0. The amino acid was collected and recrystallized from EtOH to 1.1 g. of colorless prisms, m.p. 248° (decomp.). *Anal.* Calcd. for $C_{17}H_{15}O_5N$: C, 65.17; H, 4.82; N, 4.47. Found : C, 64.81; H, 4.99; N, 4.17.

3-(3,4-Methylenedioxyphenyl)-6-methoxycarbostyril (VI)—i) From *cis*-α-(3,4-methylenedioxyphenyl)-2-nitro-5-methoxycinnamic acid (IV) : A solution of 0.05 g. of *cis*-nitrocinnamic acid (IV) in 1 cc. of 5% NH_4OH was added into a mixture of 0.2 g. of $FeSO_4 \cdot 7H_2O$ in 1 cc. of water and 1 cc. of 28% NH_4OH under continuous stirring. The mixture was then heated on a water bath for 20 min. and filtered. The filtrate and the washings from $Fe(OH)_3$ were combined, neutralized with conc. HCl, and extracted with benzene. After drying the benzene layer, the solvent was removed and the residue was recrystallized from EtOH to 0.03 g. of colorless plates, m.p. 280~282° (decomp.). *Anal.* Calcd. for $C_{17}H_{13}O_4N$: C, 69.14; H, 4.44; N, 4.74. Found : C, 69.04; H, 4,32; N, 4.34.

ii) From *trans*-α-(3,4-methylenedioxyphenyl)-2-amino-5-methoxycinnamic acid (V) : A mixture of 0.1 g. of aminocinnamic acid (V) and 10 cc. of dehyd. EtOH was refluxed for 10 hr. After evaporation of the solvent, the residue was recrystallized from EtOH to 0.06 g. of colorless plates, m.p. 280~282° (decomp.), which showed no depression when mixed with a specimen prepared by the method (i).

Attempted Pschorr Reaction of *trans*-α-(3,4-Methylenedioxyphenyl)-2-amino-5-methoxycinnamic Acid (V) in MeOH—One g. of aminocinnamic acid (V) in 20 cc. of MeOH with 12.5 cc. of 20% H_2SO_4 was diazotized at 0° with 10 cc. of *N* $NaNO_2$. After 30 min. at 0°, the orange solution was diluted with 15 cc. of water and 3 g. of Gattermann Cu was added in small portions under continuous stirring. The mixture was warmed on a water bath until a diazo-coupling test became negative. The cooled mixture was neutralized with Na_2CO_3 and extracted with AcOEt. After drying, the solvent was removed and the residue was recrystallized from EtOH to 0.3 g. of light yellow prisms, m.p. 226° (decomp.). *Anal.* Calcd. for $C_{34}H_{28}O_{10}N_2$: C, 65.38; H, 4.52; N, 4.49; CH_3O, 9.94. Found : C, 65.67; H, 4.90; N, 4.62; CH_3O, 9.76. IR (Nujol) cm^{-1} : $\nu_{C=O}$ 1653; δ_{N-H} 1542; ν_{C-O-C} 1249, 1038.

3-(3,4-Methylenedioxyphenyl)-6-methoxy-3,4-dihydrocarbostyril (VIII)—A solution of 0.34 g. of *trans*-nitrocinnamic acid (III) in 10 cc. EtOH was hydrogenated at atmospheric pressure in the presence of Pd-C catalyst. The theoretical amount of H_2 (4 moles) was absorbed in 10 min. After removal of the catalyst, the solvent was distilled off and the residue was recrystallized from EtOH to 0.22 g. of colorless needles, m.p. 202°. *Anal.* Calcd. for $C_{17}H_{15}O_4N$: C, 68.57; H, 5.07; N, 4.71. Found : C, 68.98; H, 5.45; N, 4.54.

Catalytic Reduction of 2,2′-Hydrazo-bis[α-(3,4-methylenedioxyphenyl)-5-methoxycinnamic Acid] (VII)—A solution of 0.1 g. of the bis-compound (VII) in 10 cc. of EtOH was hydrogenated at atmospheric pressure in the presence of Pd-C catalyst, 10.8 cc. of H_2 being absorbed in 2 hr. (calcd. for $3H_2$: 9.7 cc.). After hydrogenation had ceased, the catalyst was removed and the solvent was distilled off. The residue was recrystallized from EtOH to 0.06 g. of colorless needles, m.p. 202°, which showed no depression when mixed with the dihydrocarbostyril (VIII) prepared from *trans*-nitrocinnamic acid (III).

2-Methoxy-6,7-methylenedioxy-9-phenanthrenecarboxylic Acid (IX)—One g. of the *trans*-aminocinnamic acid (V) in 20 cc. of EtOH with 12.5 cc. of 20% H_2SO_4 was diazotized at 0° with 10 cc. of *N* $NaNO_2$. After 30 min. at 0°, the orange diazo solution was diluted with 15 cc. of water, 0.5 g. of NaH_2PO_2 was added, and 3 g. of Gattermann Cu was added in small portions under continuous stirring. The mixture was then warmed on a water bath until a diazo-coupling test became negative. The cooled mixture was extracted with Et_2O. After washing and drying, Et_2O solution was evaporated and the residue was recrystallized from EtOH to 0.24 g. of the phenanthrenecarboxylic acid (IX) as colorless prisms, m.p. 237~238° (decomp.). *Anal.* Calcd. for $C_{17}H_{12}O_5$: C, 68.91; H, 4.08. Found : C, 68.56; H, 3.71.

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6) S. N. Chakravarti, K. Granapati : J. Indian Chem. Soc., **14**, 4637(1937).

On evaporation of the mother liquor a trace of deaminated cinnamic acid (X) was obtained, as colorless needles, m.p. 203~204°, undepressed on admixture with authentic specimen prepared by Chakravarti's method.[6]

2-Methoxy-6,7-methylenedioxyphenanthrene(XI)–A mixture of 0.2 g. of the phenanthrenecarboxylic acid (IX), 10 cc. of quinoline, and 0.2 g. of Gattermann Cu was heated in an oil bath at 180~200° for 10 min. and at 250~260° for 20 min. The cooled mixture was diluted with Et_2O and extracted with dil. HCl until free from quinoline. The organic layer, after removal of the solvent, was dissolved in benzene and purified by chromatography over Al_2O_3. The phenanthrene from the eluate was recrystallized from EtOH to colorless prisms, m.p. 178°. Yield, 0.02 g. *Anal.* Calcd. for $C_{16}H_{12}O_3$: C, 75.18; H, 4.80. Found: C, 74.86; H, 4.65. UV λ_{max}^{EtOH} mμ (log ε): 254(4.52), 268(4.11), 285(4.00), 340(3.20), 356(3.24).

Picrate: Brick-red needles (from EtOH), m.p. 139~141°(decomp.).

***trans*-α-(2-Bromo-4,5-methylenedioxyphenyl)-2-nitro-5-methoxycinnamic Acid (XII)**—This compound was prepared from 0.9 g. of the aldehyde (II), 1.4 g. of sodium 6-bromohomopiperonylate, and 10 cc. of Ac_2O in the same manner as for (III) and (IV). Yield, 0.9 g. of colorless plates (from EtOH), m.p. 198~199°. *Anal.* Calcd. for $C_{17}H_{12}O_7NBr$: C, 48.36; H, 2.87; N, 3.32. Found: C, 48.30; H, 3.01; N, 3.70.

Occasionally, on recrystallization, this acid changes into yellow prisms which melts at 203°, suggesting dimorphism. Similar pair of isomers have been obtained by May, *et al.*[7] in analogous cinnamic acid.

***trans*-α-(2-Bromo-4,5-methylenedioxyphenyl)-2-amino-5-methoxycinnamic Acid (XIII)**—This material was obtained from 1 g. of the nitrocinnamic acid (XII), 15 cc. of 28% NH_4OH, and 4.4 g. of $FeSO_4 \cdot 7H_2O$ in the same manner as for (V). Yield, 0.8 g., yellow prisms, m.p. 229~230°(decomp.) (from EtOH). *Anal.* Calcd. for $C_{17}H_{14}O_5NBr$: C, 52.06; H, 3.60; N, 3.57. Found: C, 52.18; H, 3.20; N, 3.40.

3-(2-Bromo-4,5-methylenedioxyphenyl)-6-methoxycarbostyril (XIV)—This compound was synthesized by the same procedure as for (VI)(ii) starting from 0.1 g. of *trans*-aminocinnamic acid (XIII) and 10 cc. of dehyd. EtOH. Yield, 0.06 g. of colorless needles (from Et_2O), m.p. 265°. *Anal.* Calcd. for $C_{17}H_{12}O_4NBr$: C, 54.56; H, 3.23; N, 3.74. Found: C, 54.60; H, 3.01; N, 4.10.

1-Bromo-3,4-methylenedioxy-7-methoxy-10-phenanthrenecarboxylic Acid (XV)—A mixture of 0.5 g. of the bromo-aminocinnamic acid (XIII), 10 cc. of EtOH, and 6 cc. of 20% H_2SO_4 was diazotized at 0° with 10 cc. of *N* $NaNO_2$. The mixture was stirred for 30 min. at 0° to complete diazotization. After dilution with 7 cc. of water, 1.5 g. of Gattermann Cu was added in small portions under continuous stirring and a violent evolution of nitrogen occurred. The mixture was then heated gently on a water bath until no more nitrogen evolved. The mixture was cooled and the acid was collected. By reprecipitation from its basic solution with dil. HCl it was obtained as an amorphous powder. Yield, 0.2 g. This material was subjected to the next step without further purification.

2-Methoxy-5,6-methylenedioxy-9-phenanthrenecarboxylic Acid (XVI)—A mixture of 0.1 g. of the bromophenanthrenecarboxylic acid (XV), 6 cc. of *N* NaOH, 2 cc. of EtOH, and 0.4 g. of Wohl Zn[8] was refluxed for 24 hr. After cool, the mixture was filtered and then acidified with conc. HCl. The precipitate was recrystallized from EtOH to colorless prisms, m.p. 232~235°. Yield, 0.04 g. *Anal.* Calcd. for $C_{17}H_{12}O_5$: C, 68.91; H, 4.08. Found: C, 69.25; H, 4.54.

2-Methoxy-5,6-methylenedioxyphenanthrene (XVII)—This substance was prepared from 0.04 g. of the phenanthrenecarboxylic acid (XVI), 2 cc. of quinoline, and 0.05 g. of Gattermann Cu in the same manner as for (XI). Yield, 0.01 g. of colorless prisms, m.p. 130~131°. *Anal.* Calcd. for $C_{16}H_{12}O_3$: C, 75.18; H, 4.80. Found: C, 74.88; H, 5.26. UV λ_{max}^{EtOH} mμ (log ε): 234(4.40), 253(4.60), 266(4.61), 288(4.15), 344(3.18), 362(2.99).

Picrate: Brick-red needles (from EtOH), m.p. 140~141°(decomp.).

The authors express their deep gratitude to Prof. M. Tomita of the Kyoto University for his guidance. Thanks are due to Dr. K. Hozumi and Misses F. Tanase and M. Kamenori of the Elementary Analysis Center of the Kyoto University, and to Mrs. M. Hasegawa and Mr. T. Ueda of this school for carrying out the microanalyses. The authors also wish to thank Mr. K. Machida and Miss I. Uchida, Faculty of Pharmacy, Kyoto University, for the measurements of infrared spectra.

Summary

In a study on phenanthrene series, 2-methoxy-5,6-methylenedioxyphenanthrene (XVII) and 2-methoxy-6,7-methylenedioxyphenanthrene (XI) were prepared through the condensation of 2-nitro-5-methoxybenzaldehyde (II) with sodium salt of 6-bromohomopiperonylic acid or homopiperonylic acid (I) as the starting materials. (Received December 9, 1959)

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7) E. L. May, E. Mosettig: J. Org. Chem., **11**, 627(1946).
8) A. Wohl: Ger. Pat. 84,891.