Action of Hydrobromic Acid on Retene (XIII).—Five grams of retene (m.p. 97.5–99.5°) (XIII) was refluxed for 96 hours in a mixture containing 100 ml. of glacial acetic acid and 50 ml. of concentrated hydrobromic acid. The product which separated on cooling yielded 3.67 g. (73%) of pink platelets, m.p. 95–98°, which did not depress the melting point of retene. Further concentration yielded an additional 0.85 g. of slightly less pure material.

DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XXXIII.[1] 2,7-Disubstituted Phenanthrenes[2,3]

BY CHARLES K. BRADSHER, LEO E. BEAVERS[4] AND NIICHIRO TOKURA

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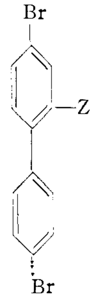
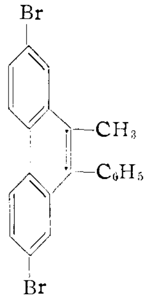
Starting in each case with biphenyl derivatives prepared from suitably substituted fluorenones, 2,7-dibromo-9-methyl-10-phenyl- and 2,7-dimethoxy-9-ethyl-10-(*p*-methoxyphenyl)-phenanthrene have been prepared by the aromatic cyclodehydration method. Some new derivatives of 2',4'-dimethoxybiphenyl-2-carboxylic acid have been prepared.

In earlier papers[5,6] it was pointed out that 9-phenylphenanthrene may be regarded as a closed model of the physiologically active[7,8] triphenylethylene system. As part of a continuation of this study we have undertaken the preparation of two 9-phenylphenanthrene derivatives bearing substituents in both of the terminal rings of the phenanthrene nucleus. This represents the first attempt to prepare such terminally disubstituted phenanthrenes by aromatic cyclodehydration, although monosubstituted analogs were prepared earlier by this method.[5,9]

As a starting material 4,4'-dibromobiphenyl-2-carboxylic acid (I) was used. The methyl ester II was reduced with lithium aluminum hydride (89% yield), and the resulting carbinol III treated with phosphorus tribromide to yield the bromide IV. Treatment of the bromide with potassium cyanide in ethanol–water afforded a mixture containing the nitrile V (82%) and the corresponding amide VI (3.5%). The nitrile V was alkylated in the usual way using methyl iodide, and the resulting nitrile VII treated with phenylmagnesium bromide affording the expected ketone VIII. When the ketone VIII was refluxed for one week with the usual hydrobromic–acetic acid mixture, only a small quantity of the expected cyclization product was obtained,[10] and this was very difficult to separate from unchanged starting material. Much better results (83.5%) were obtained using concentrated sulfuric acid as the cyclizing medium. The over-all yield from the 4,4'-dibromobiphenyl-2-carboxylic acid (I) was 29%. The new 2,7-dibromo-9-methyl-10-phenylphenanthrene (IX) is a colorless crystalline solid, m.p. 127–127.5°.

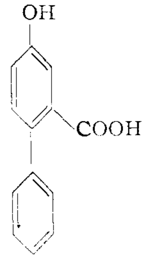
I, Z = COOH
II, Z = $COOCH_3$
III, Z = CH_2OH
IV, Z = CH_2Br
V, Z = CH_2CN
VI, Z = CH_2CONH_2
VII, Z = $CH(CH_3)CN$
VIII, Z = $CH(CH_3)COC_6H_5$



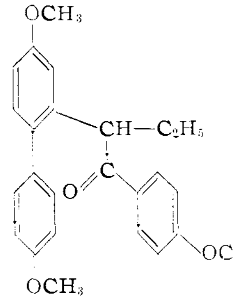


IX

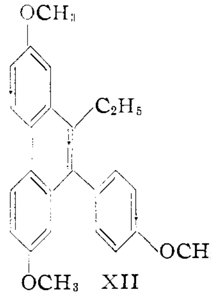
Similar methods were used in the preparation of 2,7-dimethoxy-9-ethyl-10-(*p*-methoxyphenyl)-phenanthrene (XII) starting from the known 4,4'-dihydroxy-2-biphenylylcarboxylic acid (X). This, like the analogous dibromo acid I, was pre-



X



XI



XII

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[1] For the preceding communication of this series see THIS JOURNAL, **78**, 3193 (1956).

[2] This investigation was supported in part by a research grant (C-1743) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

[3] Abstracted in part from a thesis submitted by Leo E. Beavers in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1955.

[4] Public Health Service Research Fellow of the National Institutes of Health (1952–1954).

[5] C. K. Bradsher and W. J. Jackson, Jr., THIS JOURNAL, **74**, 4880 (1952).

[6] C. K. Bradsher and D. J. Beavers, *ibid.*, **78**, 2153 (1956).

[7] E. C. Dodds, L. Goldberg, E. I. Grunfeld, W. Lawson, C. M. Saffer and R. Robinson, *Proc. Roy. Soc. (London)*, **B132**, 83 (1944).

[8] G. M. Badger, L. A. Elson, A. Haddow, C. L. Hewett and M. Robinson, *ibid.*, **B130**, 255 (1941).

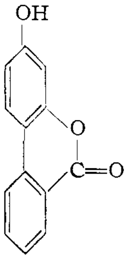
[9] C. K. Bradsher and L. J. Wissow, THIS JOURNAL, **68**, 1094 (1946).

[10] The slow rate of cyclization could be predicted from the known deactivating influence of a halogen substituent upon an aromatic nucleus. A similar effect was observed on cyclizing *meta* to a chlorine substituent (ref. 9).

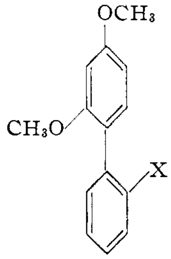
pared from fluorene. The phenolic hydroxyl groups were methylated and the resulting dimethoxy acid reduced directly with lithium aluminum hydride without previous esterification. The analog of V was alkylated with ethyl bromide and the resulting nitrile treated with *p*-methoxyphenylmagnesium bromide to afford the ketone XI.

Despite the fact that cyclization of XI had to occur in an unfavorable position,[11] *meta* to a methoxyl group, it was found that in polyphosphoric acid at 150° a 65% yield of the desired phenanthrene XII could be obtained.

Comparable experiments beginning with the readily available[12,13] lactone of 2′,4′-dihydroxybiphenyl-2-carboxylic acid (XIII) and proceeding *via* 2,4′-dimethoxybiphenylyl-2-carboxylic acid (XIV) were carried as far as the biphenylylacetonitrile XVII. Since it seems unlikely that further work will be done on this system in the near future, details of these experiments have been included.



XIII



XIV, X = COOH
XV, X = COOCH₃
XVI, X = CH₂OH
XVII, X = CH₂CN

Experimental

4,4′-Dibromobiphenyl-2-carboxylic Acid (I).—Ten grams of crude 2,7-dibromofluorenone[14] (prepared in 100% yield by oxidation of 2,7-dibromofluorene) was suspended in 150 ml. of diphenyl ether and heated. At about 80° the ketone dissolved and 10 g. of solid potassium hydroxide went into solution rapidly at about 100° and a precipitate began to form immediately. The heating bath was kept at 160–165° for 40 minutes and then the precipitate was collected on a filter containing a Hyflo bed and washed with benzene. The mixture of salts and Hyflo was stirred with 100 ml. of hot water and the hot mixture filtered. The colorless filtrate was acidified and the finely divided acid collected and dried. The crude acid weighed 9.6 g. (91%), m.p. 219–219.5°. Recrystallized from methanol it was obtained as colorless needles, m.p. 219–219.5° (lit.[15] 212°).

Methyl Ester of 4,4′-Dibromobiphenyl-2-carboxylic Acid (II).—The acid (11.9 g.) was esterified by refluxing for 12 hours in 300 ml. of methanol containing 8 ml. of concentrated sulfuric acid. After 250 ml. of the methanol had been distilled off the residue was taken up in ether and the solution washed, dried and concentrated. On standing overnight the residual oil solidified yielding 12.2 g. (99%) of the crude ester suitable for reduction, m.p. 47–52°. The analytical sample consisted of slender colorless prisms, m.p. 52.5–54°.

Anal. Calcd. for $C_{14}H_{10}Br_2O_2$: C, 45.44; H, 2.72. Found[16]: C, 45.68; H, 2.94.

4,4′-Dibromo-2-biphenylylcarbinol (III).—Lithium aluminum hydride (3.1 g.) was dissolved in 300 ml. of anhydrous ether with mechanical stirring and a solution containing 12.2 g. of the crude ester (m.p. 47–52°) in 200 ml. of dry ether added at such a rate as to maintain rapid reflux. Refluxing was continued for an additional half-hour, then the complex was decomposed by addition of 6 *M* sulfuric acid. The ethereal layer was separated, washed, dried over magnesium sulfate, and concentrated. The solid colorless residue was recrystallized from methanol–water as tiny colorless needles, m.p. 134–136°, 10 g. (89%). The analytical sample melted at 137.5–138°.

Anal. Calcd. for $C_{13}H_{10}Br_2O$: C, 45.65; H, 2.95. Found: C, 45.78; H, 3.10.

4,4′-Dibromo-2-biphenylylbromomethane (IV).—The carbinol (10 g.) was dissolved in 100 ml. of anhydrous ether and cooled in ice while 2.7 g. of phosphorus tribromide was added in small portions. After the mixture had stood in the ice-bath for 8 hours and at room temperature for 14 hours 1 ml. of methanol was added to destroy the excess phosphorus tribromide. The ether solution was washed with water and bicarbonate, dried and concentrated. The residue crystallized from benzene–ligroin as small white prisms, m.p. 146–146.5°, yield 11.4 g. (97%). The analytical sample melted at 149–149.3°.

Anal. Calcd. for $C_{13}H_9Br_3$: C, 38.55; H, 2.24. Found: C, 38.91; H, 2.47.

α-(4,4′-Dibromo-2-biphenylyl)-acetonitrile (V).—The bromomethane derivative (11.7 g.) was dissolved in 350 ml. of ethanol with heating and 2.95 g. of potassium cyanide added in 10 ml. of water. Refluxing was continued for 5.5 hours after which 200 ml. of ethanol was distilled off. The concentrated solution was diluted with water and the solid which precipitated was collected, washed with water, and dried. The dry solid was dissolved in benzene and the solution concentrated to 100 ml. and allowed to crystallize. Filtration removed 0.4 g. (3.5%) of fine white needles, m.p. 213–214°.

The benzene solution was concentrated to about 50 ml., ligroin added, and crystallization allowed to proceed. The product 8.25 g. (82%) was a colorless solid, m.p. 118–123°, pure enough for further reactions. An analytical sample melted at 125.3–125.6°.

Anal. Calcd. for $C_{14}H_9Br_2N$: C, 47.89; H, 2.58. Found: C, 47.87; H, 2.77.

The fine white needles, m.p. 213–214°, isolated as by-product melted at 213–213.5° when recrystallized and appear to be α-(4,4′-dibromo-2-biphenylyl)-acetamide (VI).

Anal. Calcd. for $C_{14}H_{11}Br_2NO$: C, 45.56; H, 3.00. Found: C, 45.50; H, 2.96.

α-(4,4′-Dibromo-2-biphenylyl)-propionitrile (VII).—Sodium amide[17] was prepared in liquid ammonia from 0.58 g. of sodium. After addition of 50 ml. of ether the ammonia was allowed to evaporate. A solution of 7.1 g. of α-(4,4′-dibromo-2-biphenylyl)-acetonitrile (V) in 300 ml. of ether was added slowly with stirring. The solution was refluxed for one-half hour after completion of the addition.

To the dark brown solution a solution containing 6 g. of methyl iodide in 25 ml. of dry ether was added dropwise. There was a mild exothermic reaction and the solution became yellow. After addition of 20 ml. of dry ether stirring was continued for 14 hours at room temperature. At the end of this period the reaction mixture was poured into ice and dilute sulfuric acid. The ethereal layer was washed (sodium bicarbonate solution), dried and evaporated. The residue was crystallized from benzene–ligroin yielding 5.7 g. (77%) of crystals, m.p. 102–103°. The analytical sample melted at 102.2–103.2°.

Anal. Calcd. for $C_{15}H_{11}Br_2N$: C, 49.32; H, 3.03. Found: C, 49.27; H, 2.90.

α-(4,4′-Dibromo-2-biphenylyl)-propiophenone (VIII).—To a Grignard reagent prepared in ether from 36.1 g. of bromobenzene, 40 g. of α-(4,4′-dibromo-2-biphenylyl)-propionitrile dissolved in 800 ml. of anhydrous ether was added slowly. After the addition was complete, the mixture was refluxed for 9 hours then cooled in an ice-bath while 50 ml. of 2 *M* hydrochloric acid was added. The ether was distilled and replaced by 800 ml. of 2 *M* hydrochloric acid. The acid suspension was heated with stirring for three hours on the steam-bath. The crystalline material thus formed was collected, washed and dried. The solid was recrystallized from methanol (Norite) yielding 30.4 g. (64%) of

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[11] *Cf.* G. D. Graves and R. Adams, THIS JOURNAL, **45**, 2439 (1932); J. H. Gardner and R. Adams, *ibid.*, **45**, 2455 (1923); R. A. Jacobson and R. Adams, *ibid.*, **46**, 1312 (1924); L. F. Fieser and C. K. Bradsher, *ibid.*, **58**, 1738 (1936); E. Thielepape, *Ber.*, **55**, 127 (1922).

[12] W. Robert and H. Huntley, *J. Chem. Soc.*, 1870 (1929).

[13] R. Adams, D. C. Pease, J. H. Clark and B. R. Baker, THIS JOURNAL, **62**, 2197 (1940).

[14] A. Werner and A. Egger, *Ber.*, **37**, 3026 (1904).

[15] J. Holm, *ibid.*, **16**, 1081 (1883).

[16] All analyses by Micro-Tech Laboratories.

[17] R. Levine and C. R. Hauser, THIS JOURNAL, **68**, 760 (1946).

glistening light yellow needles, m.p. 131–131.5°. The analytical sample was colorless, m.p. 131.2–132°.

Anal. Calcd. for $C_{21}H_{16}Br_2O$: C, 56.78; H, 3.63. Found: C, 57.01; H, 3.81.

2,7-Dibromo-9-methyl-10-phenylphenanthrene (IX).—Five grams of the ketone VIII was finely powdered and slowly added to 200 ml. of concentrated sulfuric acid with rapid stirring. The ketone dissolved almost completely and a white substance began to precipitate from the greenish-blue solution. The solution was stirred mechanically for six hours at room temperature and then poured over ice. The crude solid was collected and crystallized from benzene–alcohol as small colorless prisms, m.p. 126.5–127.5°, yield 4 g. (83.5%). The analytical sample melted at 127–127.5°.

Anal. Calcd. for $C_{21}H_{14}Br_2$: C, 59.18; H, 3.31. Found: C, 58.94; H, 3.40.

4,4′-Dimethoxybiphenyl-2-carboxylic Acid.—Seven grams of 4,4′-dihydroxybiphenyl-2-carboxylic acid (X), prepared from fluorene by the method of Courtot,[18] was refluxed for 10 hours with a mixture consisting of 20 g. of sodium hydroxide, 80 ml. of water and 20 g. of dimethyl sulfate. The gray precipitate obtained upon acidification was recrystallized from dilute ethanol as colorless needles, m.p. 153–154°, yield 5.0 g. (64%).

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.61; H, 5.67.

4,4′-Dimethoxy-2-biphenylylcarbinol.—Seven grams of 4,4′-dimethoxybiphenyl-2-carboxylic acid was placed in the thimble of a Soxhlet extractor and extracted into a flask containing 6 g. of lithium aluminum hydride in 100 ml. of ether. After eight hours the reaction mixture was worked up as in the case of III. The product crystallized from methanol as colorless needles, m.p. 88–89°, yield 5.0 g. (75.5%).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.99; H, 6.65.

α-(4,4′-Dimethoxy-2-biphenylyl)-acetonitrile.—Five grams of dimethoxybiphenylcarbinol was converted to the bromomethane derivative by the action of 5 ml. of phosphorus tribromide. Worked up as in the case of IV, 4.5 g. of colorless flakes, m.p. 81–82°, was obtained by evaporation of the ether. This material was not purified further, but dissolved in 100 ml. of ethanol; 10 g. of potassium cyanide in 50 ml. of water was added and the mixture stirred for 12 hours at 40–45°, followed by refluxing for one-half hour.

After evaporation of the ethanol the residue was taken up in methylene chloride the solution washed, dried and evaporated. Distillation of the residue *in vacuo* yielded 3.0 g. (58%) of a yellow oil, b.p. 195–205° (5 mm.), which solidified to white flakes, m.p. 51–52°.

The analytical sample, b.p. 200–203° (5 mm.), was not recrystallized.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.75; H, 6.15.

α-(4,4′-Dimethoxy-2-biphenylyl)-butyronitrile.—Three grams of the dimethoxybiphenylylacetonitrile (above) was alkylated by the action of sodium amide (from 1 g. of sodium) and ethyl bromide (10 ml.). The product was worked up as in the case of VII except that purification was accomplished through vacuum distillation. The product was a viscous orange oil, b.p. 204–210° (6 mm.), yield 2.5 g. (75%). The analytical sample, $n^{25}D$ 1.5853, b.p. 208–210° (6 mm.), probably contained some of the starting material.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81. Found: C, 76.39; H, 6.75.

α-(4,4′-Dimethoxy-2-biphenylyl)-4-methoxybutyrophenone (XI).—A Grignard reagent was prepared in ether from 7 g. of *p*-bromoanisole. To this 2.5 g. of the dimethoxybiphenylylbutyronitrile (above) was added in 25 ml. of ether and the mixture refluxed for 12 hours. The reaction mixture was decomposed with dilute hydrochloric acid, the ether evaporated, and the residual acid mixture refluxed for a half hour. The organic material was taken up in ether and the ethereal solution washed, dried, evaporated and the residue distilled under reduced pressure. The brown viscous liquid ($n^{25}D$ 1.5870) was analytically pure, b.p. 230–240° (5 mm.), yield 0.8 g. (23%).

Anal. Calcd. for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 76.80; H, 7.09.

2,7-Dimethoxy-9-(*p*-methoxyphenyl)-10-ethylphenanthrene (XII).—To 10 g. of polyphosphoric acid[19] 0.8 g. of the ketone XI was added and the mixture stirred at 150° for one-half hour. The reaction mixture was poured on ice and extracted with ether. The washed and dried ethereal solution on concentration afforded orange flakes which on recrystallization from ethanol and acetic acid gave colorless micro-crystals, m.p. 184–185°, yield 0.50 g. (65.5%). The ultraviolet spectrum resembled 9-phenylphenanthrene; λ_{max} and (log ϵ): 227 (4.38), 262 (4.79), 271 (shoulder) (4.51), 285 (4.26), 297 (shoulder) (4.10), and 302 (shoulder) (4.00); $\lambda_{min.}$ 236 (4.28) and 281 mμ (4.24).

Anal. Calcd. for $C_{25}H_{24}O_3$: C, 80.62; H, 6.50. Found: C, 80.27; H, 6.77.

2′,4′-Dimethoxybiphenyl-2-carboxylic acid (XIV) was prepared by refluxing the lactone XIII[12,13] of 2′,4′-dihydroxybiphenyl-2-carboxylic acid (32 g.) with sodium hydroxide (60 g.) and methyl sulfate (75 g.) in water (300 ml.) for one week. Neutralized reaction mixture afforded 31 g. (64%) of the desired dimethoxy acid XIV, as needles from alcohol, m.p. 149–150° (lit.[12] 150°).

In some experiments a neutral fraction was obtained containing the methyl ester XV which boiled at 200–202° (4 mm.) and crystallized from ethanol as fine prisms, m.p. 56–57°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.89; H, 6.16.

2′,4′-Dimethoxy-2-biphenylylcarbinol (XVI). (A) By **Reduction of the Acid XIV.**—By the same technique employed in the reduction of the 4,4′-isomer the acid was reduced using lithium aluminum hydride. The carbinol was obtained as a colorless viscous oil, b.p. 185–195° (3 mm.), $n^{25}D$ 1.5963, yield 70.5%.

(B) By **Reduction of the Methyl Ester XV.**—The ester was reduced (81% yield) by the technique employed for the dibromo analog II.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.88; H, 6.72.

α-(2′,4′-Dimethoxy-2-biphenylyl)-acetonitrile (XVII).—Twenty grams of the carbinol XVI in dry ether was treated with phosphorus tribromide and worked up as described in the case of the analog IV. The crude bromide, once recrystallized from ethanol (m.p. 66–67°) was dissolved in ethanol and treated with potassium cyanide as in the case of the isomer. The product was obtained as a pale yellow liquid, b.p. 185–193° (3 mm.), yield 17 g. (65%). The analytical sample boiled at 190–191° (3 mm.), $n^{25}D$ 1.5874.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 76.11; H, 6.06.

DURHAM, NORTH CAROLINA

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[18] C. Courtot, *Ann. chim.*, [10] **14**, 5 (1930).

[19] We are indebted to the Victor Chemical Co. for a generous gift of polyphosphoric acid.