Syntheses of 4,5-Dialkylfluorenes

Part I. Synthesis of 4,5-Dimethylfluorene

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4,5-Dimethylfluorene and related 4,5-disubstituted fluorene derivatives were synthesized.

In a course of studying chemical structure of gibberellins, plant-growth regulating metabolites of *Gibberella fujikuroi* (Sawada) Wollenweber, Yabuta, Sumiki, Aso, Tamura, Igarashi and Tamari¹⁾ reported in 1941 that dehydrogenation of gibberellin A, gibberellin B and gibberic acid with selenium, palladium or zinc powder yielded a hydrocarbon, which was named gibberene. Gibberene was identified as a substituted-fluorene and the formula $C_{16}H_{16}$ was proposed, suggesting it might be 4-methyl-5-ethylfluorene. The present author synthesized 4,5-dimethyl and 4-methyl-5-ethylfluorenes intending to clarify the above suggestion half decade ago, but they did not agree with gibberene and reports concerning them were unpublished till to-day. In this paper syntheses of 4,5-dimethylfluorene and related compounds are described. Reaction scheme is shown in Fig. 1.

Meanwhile, Mulholland and Ward²⁾ demonstrated in 1954 that gibberene is 1,7-dimethylfluorene, $C_{15}H_{14}$, by degradation and synthesis. They³⁾ also reported in 1956 synthesis of 4,5-dimethylfluorene starting from *m*-toluic acid.

4-Methylphenanthrenequinone (II) had been synthesized by Harworth⁴⁾ and Radcliffe^{4a)} et al., but melting points of II and its quinoxaline derivative reported by them were not correct and melting points obtained by the author agreed with Aziz and Breckenridge's⁵⁾. Cleavage of quinone-ring by Linstead's method⁶⁾ using dilute hydrogen peroxide in aqueous acetic acid gave 6-methyldiphenic acid (III). III was readily oxidized with alkaline permanganate to give diphenyl-2,2',6-tricarboxylic acid (X), which in turn was converted with concentrated sulfuric acid into fluorenone-4,5-dicarboxylic acid (XI) in good yield. The melting point of X was fifty degrees lower than that of "diphenyltricarboxylic acid" obtained by Yabuta et al.¹⁾

Ring closure of acid chloride of III by warming with anhydrous aluminium chloride gave 5-methylfluorenone-4-carboxylic acid (IV). Treatment with sulfuric acid⁷⁾, one of the most usual method of ring closure of diphenic acids, failed to give satisfactory re-

4) R. Haworth, *ibid.*, **1932**, 1125.

4a) C. Radcliffe, I. Sherwood and W. Short, *ibid.*, **1931**, 2293.

5) D. Aziz and J. Breckenridge, *Can. J. Research*, **28B**, 26 (1950); *C.A.* **44**, 5850 (1950).

6) R. Linstead and A. Walpole, *J. Chem. Soc.*, **1930**, 850; R. Linstead and W. Doering, *J. Am. Chem. Soc.*, **64**, 1991 (1942).

7) C. Graebe and C. Aubin, *Ann.*, **247**, 275 (1888); E. Bergmann et al., *Bull. Soc. Chim. France*, **1951**, 669; *C.A.* **46**, 11173 (1952).

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1) T. Yabuta, Y. Sumiki, K. Aso, T. Tamura, H. Igarashi and K. Tamari, *J. Agr. Chem. Soc. Jap.*, **17**, 975 (1941).

2) T. Mulholland and G. Ward, *J. Chem. Soc.*, **1954**, 4676.

3) T. Mulholland and G. Ward, *ibid.*, **1956**, 2415.

sult in this case, because of accompanying sulfonation under condition which brought about ring closure. Since IV was resistant to oxidation with alkaline permanganate, it was difficult to obtain the dicarboxylic acid XI in reasonable yield from IV, agreeing with Mulholland's observation³⁾ who employed permanganate in pyridine. Oxidation with sodium dichromate^{7a)} in glacial acetic acid gave the lactone of 5-hydroxymethylfluorenone-4-carboxylic acid and a mixture of the starting acid IV and the dicarboxylic acid XI.

Starting from IV, 4,5-dimethylfluorenone (VI) was synthesized via two routes; reduction of methyl ester of IV with lithium aluminium hydride gave diol (V), which was hydrogenolized to give 4,5-dimethylfluorene VI. Treating IV with hydrazine hydrate in diethyleneglycol gave 5-methylfluorene-4-carboxylic acid (VIII) in good yield, but if the reaction was carried out in the presense of alkali intractable substance was formed. Reduction by Clemmensen method gave unsatisfactory result also. Reduction of acid chloride of VIII with sodium borohydride gave hydroxymethyl derivative of fluorene (IX), which in turn hydrogenolized to give 4,5-dimethylfluorene VI. The mixed melting point of VI with gibberene showed depression. Oxidation of VI gave the corresponding fluorenone derivative (VII), melting point of which was depressed on admixture with gibberenone obtained by Yabuta et al.¹⁾

EXPERIMENTAL

Melting points are uncorrected. Elementary analyses were carried out by Misses K. Kamito, I. Isobe and M. Suzuki, Microanalytical Section of Department of Agricultural Chemistry, Faculty of Agriculture, The University of Tokyo.

4-Methylphenanthrene (I). Synthesized by Bachmann's method, m.p. 52.5~53°C. Reported m.p.s.^{4,8)}

7a) Details will be reported in the following paper (Part III of this series).

8) W. Bachmann and R. Edgerton, *J. Am. Chem. Soc.*, **62**, 2219 (1940).

are 49~50°C.

The trinitrobenzoate. Yellow needles, m.p. 165.5~167°C. *Anal.* Found: C, 62.31; H, 3.73; N, 10.32. Calcd. for $C_{15}H_{12} \cdot C_6H_3N_3O_6$: C, 62.22; H, 3.73; N, 10.37%.

The trinitrofluorenone adduct. Prepared by Orchin's method⁹⁾, orange needles, m.p. 196.6~197.4°C. *Anal.* Found: C, 66.32; H, 3.41; N, 8.47. Calcd. for $C_{15}H_{12} \cdot C_{13}H_5N_3O_7$: C, 66.27; H, 3.38; N, 8.27%.

4-Methylphenanthrenequinone (II). To a stirred solution of 108.5 g (0.565 mole) of 4-methylphenanthrene in 500 ml of glacial acetic acid, maintained at 65~70°C, was added a solution of 226 g (2.26 moles) of chromic anhydride in 350 ml of glacial acetic acid and 140 ml of water over a period of 35 minutes. The temperature was kept at 62~66°C for another 45 minutes and after being cooled to room temperature the reaction mixture was poured into ice water. Orange precipitates were collected, washed thoroughly with water, subsequently with methanol and dried to give 75 g (60%) of crude product, m.p. 145~154°C. A mixture of 74 g (0.333 mole) of the above crude product, 110 g of 40% sodium hydrogen bisulfite and hot water was ground in mortar and diluted with warm water and filtered through celite to remove insoluble resinous product. Pale brown filtrate was added to concentrated sodium carbonate, and orange-yellow precipitates formed were washed with water and dried. The yield was 49.3 g (39.4%), m.p. 159~161.5°C. Recrystallization from acetic acid gave a product, m.p. 162~3°C. Reported m.p.s. are 167°C⁵⁾ and 187°C⁴⁾. *Anal.* Found: C, 80.99; H, 4.20. Calcd. for $C_{15}H_{10}O_2$: C, 81.06; H, 4.54%.

The quinoxaline derivative: M.p. 158~9°C. Reported m.p.s. are 161°C⁵⁾ and 178°C⁴⁾. *Anal.* Found: C, 85.36; H, 4.71; N, 10.05. Calcd. for $C_{21}H_{14}N_2$: C, 85.69; H, 4.79; N, 9.52%.

6-Methyldiphenic Acid (III). A mixture of 47.7 g (0.215 mole) of 4-methylphenanthrenequinone, 150 ml of glacial acetic acid, 340 ml of water and 90 ml of 30% hydrogen peroxide was gently refluxed above asbestos wire gauze for 70 minutes. Orange red colour of the quinone disappeared and small quantity of resinous product was formed. The hot mixture was filtered and allowed to cool to give a crystalline precipitate. The yield of crude product melting at 220~224°C was 37 g (67.3%). Recrystallization from acetic acid after removing neutral substance gave a

9) M. Orchin and E. Woolfolk, *J. Am. Chem. Soc.*, **68**, 1727 (1946); M. Orchin, L. Reggel and E. Woolfolk, *ibid.*, **69**, 1225 (1947).

colourless crystal melting at $228\sim 9^{\circ}\text{C}$. A run in one third scale, heating on oil bath, gave crude yield of 88%. Reported m.p. is $228\sim 9^{\circ}\text{C}^{(5)}$.

Biphenyl-2,2',6'-tricarboxylic Acid (X). To a solution of 1.0 g of 6-methyldiphenic acid in 10 ml of 2.5% sodium hydroxide was added, with stirring, 32 ml of 4% potassium permanganate (7% excess) over a period of two hours. After removing the colour of permanganate, manganese dioxide was filtered and the filtrate was acidified with hydrochloric acid to give a crystalline product which was filtered after 4 hours. The yield was 1.0 g (90%) and melted at 249.5~253°C. It was recrystallized from glacial acetic acid to give a product, m.p. 254~255.5°C. Analytical sample was dried at 100°C and 1 mm Hg for 8 hours. Analytical value agreed with a formula containing half mole of water of crystallization. *Anal.* Found: C, 61.14, 61.01, 61.03, 60.82; H, 3.71, 4.01, 4.02, 3.59. Calcd. for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52. Calcd. for $C_{15}H_{10}O_6 \cdot \frac{1}{2}H_2O$: C, 61.02; H, 3.76%.

The trimethyl ester: Prepared with diazomethane, crystallized from methanol, m.p. 85~86.2°C. *Anal.* Found: C, 65.95; H, 5.11. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%.

Fluorenone-4, 5-dicarboxylic Acid (XI). A mixture of 0.30 g of biphenyltricarboxylic acid X and 2 ml of conc. sulfuric acid was heated with shaking on a preheated oil bath, and temperature of mixture was maintained at $143\sim 151^{\circ}\text{C}$ for two minutes and $150\pm 2^{\circ}$ for eight minutes to give a deep red solution. After being cooled rapidly, it was poured onto ice, washed several times with water by hand-centrifuging. The yield weighed 0.23 g (82%), melting at $273\sim 278^{\circ}\text{C}$. Recrystallization from glacial acetic acid gave a product, melting at $276\sim 7^{\circ}\text{C}$ (decomp.). Reported *m.p.s.* are $284\sim 6^{\circ}\text{C}^{(3)}$ (correct; decomp.) and $285^{\circ}\text{C}^{(9)}$. *Anal.* Found: C, 66.54, 66.59; H, 3.11, 3.06. Calcd. for $\text{C}_{12}\text{H}_8\text{O}_5$: C, 67.17; H, 3.01%. Low figure of carbon was observed also by Kruber⁽¹⁰⁾ and Mulholland⁽³⁾.

The dimethyl ester: Prepared with diazomethane, m.p. 188.5~9°C. Reported m.p. is 189~90°C (corr.)³⁹. *Anal.* Found: C, 68.83, 68.89; H, 4.39, 4.32. Calcd. for C₁₇H₁₂O₆: C, 68.91; H, 4.08%.

Attempted Oxidation of 5-Methylfluorenone-4-carboxylic Acid (IV) To a stirred solution of 0.6 g of 5-methylfluorenone-4-carboxylic acid IV (m.p. 191~2°C) described below in 5 ml of 2.5% aqueous sodium

10) O. Kruber, *Ber.*, **67**, 1000 (1934).

hydroxide was added 1.0 g (125%) of potassium permanganate in 30 ml of water at 75~80°C over a period of 70 minutes. Permanganate was consumed and the mixture was filtered and acidified with hydrochloric acid to give a 0.5 g of pale yellow crystal, contracting at 189°C and melting at 192.5~194.5°C. Recrystallization from glacial acetic acid gave a 0.3 g of product, contracting at 192.5°C and melting at 194.5~195.5°C. Analytical value showed that the product obtained was almost unchanged starting material. *Anal.* Found: C, 74.91, 74.65; H, 4.82, 4.89. Calcd. for $C_{15}H_8O_5$ (XI): C, 67.17; H, 3.01. Calcd. for $C_{15}H_{10}O_5$ (IV): C, 75.62; H, 4.23%. Mixtures of 5-methylfluorenone-4-carboxylic acid IV and fluorenone-4,5-dicarboxylic acid XI showed no depressions of melting point and melted at intermediate temp.

5-Methylfluorenone-5-carboxylic Acid (IV). A mixture of 24 g (0.094 mole) of 6-methyldiphenic acid III and 70 ml of thionyl chloride was warmed on water bath. When formation of hydrogen chloride subsided, thionyl chloride was removed under reduced pressure, 10 ml of dry benzene was added and the latter removed under reduced pressure. To a solution of acid chloride obtained above in 120 ml of nitrobenzene, 30 g (0.225 mole, 2.2 equivalent) of anhydrous aluminium chloride was added with stirring in one portion. The temperature of reaction mixture raised from 35°C to 50°C. The mixture was warmed at 50~87°C for 7 min, at 80°C for 17 min, at 90°C for 13 min and cooled to room temperature with cold water. The deep reddish-brown reaction mixture was decomposed by pouring onto ice and hydrochloric acid, and nitrobenzene was steam distilled. Solid residue was filtered, dissolved into warm dilute sodium carbonate solution, insoluble material was filtered off, and red filtrate was neutralized until small amount of amorphous precipitate was formed (pH about 6.5), treated with active charcoal, filtered and acidified with hydrochloric acid. The precipitate formed was filtered, washed with water and dried. The yield was 18.2 g (82%), melting at 188~190°C. Recrystallization from glacial acetic acid gave yellow needles, melting at 191~2°C. In another one third scale run, warming for a shorter period, the yield of 93% was obtained. Reported³⁾ m.p. is 191~2°C (corr.). *Anal.* Found: C, 75.72; H, 4.41. Calcd. for $C_{15}H_{10}O_5$: C, 75.62; H, 4.23%.

The methyl ester: Prepared with diazomethane, m.p. 114.5~115.5°C. Reported m.p. is 112~3°C³⁾.

Anal. Found: C, 76.06, 76.05; H, 5.07, 4.97. Calcd. for $C_{16}H_{12}O_5$: C, 76.18; H, 4.80%.

4-Methyl-5-hydroxymethyl-9-fluorenone (V). To a cold suspension of 0.35 g (9.2×10^{-3} mole) of lithium aluminium hydride in absolute ether which had been refluxed for one hour previously, was added dropwise a solution of 1.6 g (6.3×10^{-3} mole) methyl 5-methylfluorenone-4-carboxylate in benzene, and refluxed for few minutes. Reaction mixture was decomposed by successive addition of wet ether, water and dilute hydrochloric acid. Ether was evaporated, and residue was recrystallized twice from methanol to give a crystal, 0.3 g, m.p. 170~171.5°C. Combined filtrate was evaporated in vacuo, to yield 1.2 g of crude material, m.p. 136~155°C. The crude material obtained was dissolved in 70 ml of dry ether and added dropwise to a solution of 17 ml of lithium aluminium hydride (0.017 g/ml) in tetrahydrofuran, and refluxed for 1 hour. After treating in the usual manner, the product obtained was recrystallized from methanol to give a crystal, 0.55 g, m.p. 168~171°C. Total yield was 0.85 g (60%). One more recrystallization from methanol gave a product, m.p. 173~4°C. *Anal.* Found: C, 79.44, 79.20; H, 6.31, 6.35. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24%.

5-Methylfluorene-4-carboxylic Acid (VIII). Twenty one point four grams (0.09 mole) of 5-methylfluorenone-4-carboxylic acid, 100 ml of diethyleneglycol and 25 ml of 80% hydrazine hydrate were mixed in this order in distilling flask and heated on oil bath. Soon formation of hydrazone was observed and when water and excess of hydrazine hydrate were removed by distillation and temperature of reaction mixture reached to 170°C, formation of nitrogen began. After being kept at 175~200°C for 10 minutes and 200±2°C for 30 minutes, the clear reaction mixture was cooled, diluted with equal volume of water and poured into dilute hydrochloric acid. White precipitate formed was filtered, washed with water and dried to give a product, 19.8 g (98%), m.p. 164~8°C. For purification, a small amount of neutral substance was removed in the usual manner and recrystallized from ethanol to give a product, m.p. 168~9°C. Analytical value of sample, dried at 100°C and 1 mm g for 8 hours showed low figure of carbon. *Anal.* Found: C, 79.23, 79.47, 79.48; H, 5.91, 5.64, 5.55. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39%.

The methyl ester: Prepared with diazomethane, recrystallized from methanol, m.p. 66~8°C. *Anal.*

Found: C, 80.21, 80.35; H, 5.66, 5.54. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92%.

4-Methyl-5-hydroxymethylfluorene (IX). To a suspension of 3.6 g (0.015 mole) of 5-methylfluorene-4-carboxylic acid in absolute ether was added 3.3 g (0.0275 mole) of thionyl chloride and two drops of pyridine and the mixture was left to stand at room temperature for one and half hour with occasional swirling. After filtration, solvent and excess of reagent were removed in vacuo, 5 ml of dry benzene was added, the latter was removed in vacuo (bath temperature not exceeding 40°C). Pale yellow colored acid chloride was obtained in this manner. To a solution of 1.6 g (large excess) of sodium borohydride in aqueous ethanol was added dropwise a solution of the acid chloride obtained above in purified dioxane. Reaction took place with evolution of heat and the mixture was stirred for additional 10 minutes. Excess of hydride was decomposed with acetic acid, diluted with water and precipitates formed was extracted with ether. After treatment as in the usual manner, quantitative crude yield was obtained. Recrystallization from benzene gave 2.9 g (86%) of product, m.p. 119~119.5°C. *Anal.* Found: C, 85.58; H, 6.73. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71%.

4,5-Dimethylfluorene (VI).

a) Hydrogenolysis of 4-Methyl-5-hydroxymethylfluorene (IX). A suspension of 1 g of 10% palladium chloride on carbon in 25 ml of methanol was reduced in hydrogen atmosphere with shaking. 2.4 g (0.011 mole) of 4-methyl-5-hydroxymethylfluorene IX in 35 ml of methanol was added and catalytically reduced with shaking. Hydrogen absorbed amounted to about 110% of the theoretical. After evaporation of filtrate in vacuo, recrystallization from methanol gave a product, 1.8 g, m.p. 84.5~5°C. Residue, obtained by evaporation of the filtrate, was dissolved in *n*-hexane and chromatographed on alumina and eluted with the same solvent and 0.2 g of colourless crystal melting at 84~5°C was obtained. Total yield was 2.0 g (90%). Reported m.p.³⁰ is 81~2°C.

The trinitrobenzoate: Prepared from equimolecular proportions of 1,3,5-trinitrobenzene and 4,5-dimethylfluorene in hot ethanol, yellow needles, m.p. 117~8°C. Analytical value showed this is 1 : 1 adduct. Reported m.p.³⁰ is 114°C. *Anal.* Found: C, 61.88, 61.88; H, 3.95, 4.13; N, 10.27. Calcd. for $C_{15}H_{14} \cdot C_6H_3N_3O_6$: C, 61.91; H, 4.21; N, 10.32%.

The trinitrofluorenone adduct: Prepared from

equimolecular proportions of 2,4,7-trinitrofluorenone and the hydrocarbon in benzene-ethanol by Orchin's method³⁰, orange needles, m.p. 117~8°C. *Anal.* Found: C, 65.95; H, 3.75; N, 8.49. Calcd. for $C_{28}H_{10}N_3O_7$: C, 66.01; H, 3.76; N, 8.25%.

The tetranitrofluorenone adduct: Prepared from equimolecular proportions of 2,4,5,7-tetranitrofluorenone and the hydrocarbon in glacial acetic acid by Newman's method¹¹, deep red needles, m.p. 198~9°C. *Anal.* Found: C, 60.58; H, 3.26; N, 10.23. Calcd. for $C_{28}H_{10}N_4O_8$: C, 60.65; H, 3.27; N, 10.11%.

b) Hydrogenolysis of 4-methyl-5-hydroxymethylfluorene-9-ol (V). A mixture of 0.5 g of 4-methyl-5-hydroxymethylfluorene-9-ol and 0.1 g of 11% palladium chloride on carbon in 40 ml of methanol was shaken under 2.5~3.0 atm. pressure of hydrogen for 50 minutes. The catalyst was filtered and washed with ether and combined filtrate evaporated in vacuo. Recrystallization from methanol gave a crystal, 0.34 g (80%), m.p. 84~5°C. A run in which reduction was carried out at atmospheric pressure in glacial acetic acid gave a similar result.

4,5-Dimethylfluorenone (VII). To a hot solution of 1.0 g (5×10^{-3} mole) of 4,5-dimethylfluorene in acetic acid was added a mixture of 2.5 g (8.3×10^{-3} mole) of sodium bichromate dihydrate, 5 ml of glacial acetic acid and 1 ml of water in a period of three minutes and refluxed for two and half hour. After cooling, diluted with water and extracted with ether. Neutral fraction obtained in the usual manner weighed 0.8 g. Recrystallization from ethanol-*n*-hexane gave 0.7 g of yellow crystals, m.p. 120~121.5°C. Reported m.p. is 117~9°C³⁰.

The oxime: Prepared in pyridin by Bachmann's method¹², recrystallized from ethanol, m.p. 217.5~218.5°C. *Anal.* Found: N, 6.32. Calcd. for $C_{15}H_{13}NO$: N, 6.27%.

The 2,4-dinitrophenylhydrazones: Prepared in the usual manner, m.p. 252°C. *Anal.* Found: C, 64.62, 64.90; H, 3.81, 4.07; N, 14.45, 14.30. Calcd. for $C_{21}H_{16}N_4O_4$: C, 64.94; H, 4.15; N, 14.43%.

The semicarbazones: Prepared in the usual manner, was recrystallized from ethanol, m.p. 201~3°C. *Anal.* Found: C, 72.03; H, 5.71; N, 15.50. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84%.

11) M. Newman and W. Lutz, *J. Am. Chem. Soc.*, **78**, 2469 (1956).

12) W. Bachmann and C. Boatner, *ibid.*, **58**, 2097 (1936).

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