Syntheses of 4,5-Dialkylfluorenes

Part II. Synthesis of 4-Methyl-5-ethylfluorene (part 1)

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4-Methyl-5-ethylfluorene and related compounds were synthesized starting from 5-methylfluorene-4-carboxylic acid. The carbonyls on 4-position in 5-methyl-4-acetylfluorene and the corresponding fluorenone were found to be moderately hindered sterically.

Assumption¹⁾ that gibberene, the dehydrogenation product of gibberellins, might be 4-methyl-5-ethylfluorene prompted the author to synthesize the above compound and 4,5-dimethylfluorene. In the previous paper²⁾, the synthesis of 4,5-dimethyl fluorene was reported. 4-Methyl-5-ethylfluorene³⁾ was synthesized through two routes, and the first route starting from 5-methylfluorene-4-carboxylic acid (II) is described in this paper. Reaction scheme is shown in Fig. 1. The second route will appear in the following paper^{3a)}.

In order to increase one carbon atom, the acid chloride of 5-methylfluorene-4-carboxylic acid²⁾ (II) was converted by dimethylcadmium into a methyl ketone, 5-methyl-4-acetylfluorene (III). Reduction of III with lithium aluminium hydride or sodium borohydride gave an oil, 4-methyl-5-(α -hydroxyethyl) fluorene (V), which was catalytically reduced to give 4-methyl-5-ethylfluorene (VI), which was obtained also as an oil. Oxidation of VI

gave the corresponding solid fluorenone, 4-methyl-5-ethylfluorenone (VII), the Wolf-Kishner reduction of which gave the fluorene VI again. This reaction was used as one of the method of purification of the hydrocarbon VI. Trinitrobenzoate of VI had a much lower m.p. as shown in Table I, and less readily crystallizing property as compared with that of 4,5-dimethylfluorene, and was not so much suited for purification of the hydrocarbon. However, the 2,4,7-trinitrofluorenone adduct of VI had a higher m.p. and was obtained as readily crystallizing needles, which was suited for purification.

5-Methyl-4-acetylfluorenone (VI) was obtained in good yield by oxidation of the corresponding fluorene III. However, treatment of 5-methylfluorenone-4-carboxylic acid (I) through its acid chloride with large excess of dimethylcadmium gave IV directly in a low yield, probably owing to accompanying reaction of dimethylcadmium with carbonyl on 9-position. A synthesis employing equivalent proportions of reactants was not tried, accordingly a route to VI via IV was not attempted. Although 4-acetylfluorene gave a semicarbazone⁵⁾, 5-methyl-4-acetylfluorene

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

2) S. Takahashi, *This Journal*, **26**, 323 (1962).

3) Since Mulholland and Ward⁴⁾ had shown that gibberene is 1,7-dimethyl fluorene, it is not significant to correlate 4,5-dialkylfluorene with gibberene at present.

3a) S. Takahashi, *This Journal*, in press.

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

5) Details will be reported ater in this journal.

FIG. 1. Synthesis of 4-methyl-5-ethylfluorene.

TABLE I. MELTING POINTS OF FLUORENES AND THEIR MOLECULAR COMPOUNDS

Fluorene		TNB ^a) adduct		TNF ^b) adduct.
Substituent	M.p. (°C)	Ratio of hydrocarbon to TNB	m.p. (°C)	m.p. (°C)
No substituent	114~5	2 : 3	105	177~8
4-CH ₃ , 5-CH ₃	84.5~85	1 : 1	117~8	177~8
4-CH ₃ , 5-C ₂ H ₅	oil	1 : 1	61~2	134~5

a) 1,3,5-Trinitrobenzene.

b) 2,4,6-Trinitrofluorenone.

III gave neither semicarbazone nor 2,4-dinitrophenylhydrazone, at least under ordinary experimental conditions, but gave an oxime. III was hardly reduced by aluminium isopropylate and completely negative for iodoform test of methylketones. 5-Methyl-4-acetylfluorenone IV gave only mono-semicarbazone and test of methylketones was also negative. The property of the two ketones mentioned above reminded us of the instance of acetomesitylene, which on reaction with alkaline hypohalite, gives tri-

haloacethylmesitylene, but the latter is not cleaved by alkali⁶⁾, and forms no oxime⁷⁾ under usual conditions. Therefore it follows that the carbonyl on 4-position in III and IV is sterically hindered moderately, but hindrance is less than in the case of acetomesitylene.

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.

5-Methyl-4-acetylfluorene (III). To a solution of methylmagnesium iodide reagent in ether, prepared from 0.17 g (7×10^{-3} mole) of magnesium under nitrogen atmosphere, was added 0.8 g of anhydrous cadmium chloride (4.4×10^{-3} mole) and the mixture was refluxed for 30 min. After most of the solvent was removed by distillation, dry benzene was added and evaporation process was repeated again with

6) R. Fuson and J. Walker, *J. Am. Chem. Soc.*, **52**, 326 (1930).7) E. Feith and S. Davies, *Ber.*, **24**, 3546 (1891).

stirring, and another dry benzene was added. A solution of acid chloride of 5-methylfluorene-4-carboxylic acid in benzene, prepared from 0.60 g (2.7×10^{-3} mole) of the acid as described in previous paper², was added to the stirred mixture stated above with cooling by water. When stirring became difficult after twenty minutes, temperature raised to 50°C and stirring was continued for further twenty minutes. The reaction mixture was cooled in an ice bath and decomposed in the usual way by the addition of ice, water and dilute hydrochloric acid. The aqueous phase was extracted with ether and combined organic layer washed successively with dilute hydrochloric acid, dilute sodium carbonate and water, dried with anhydrous sodium sulfate. After evaporating the solvent in vacuo, a small amount of ethanol was added and cooled to give 0.53 g (88%) of a crystal, m.p. 73.5~74.5°C. Recrystallization from ethanol gave a product, melting at 74~75°C. *Anal.* Found: C, 86.46; H, 6.42. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35%. In a run, in which a product was crystallized with difficulty, chromatography on alumina with hexane-benzene as eluent gave a product which was readily crystallized. Distillation also gave a good result.

The oxime: Prepared in pyridine by Bachmann's method⁹, m.p. 130~146°C. One recrystallization from aqueous ethanol gave a product, m.p. 155~169°C. *Anal.* Found: C, 80.90; H, 6.28; N, 5.59. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.39; N, 5.90%.

Attempted formation of the semicarbazone of III: A mixture of 22 mg (1×10^{-4} mole) of the methylketone III, 0.055 ml (1.1×10^{-4} mole) of a stock solution (0.01 mole/5 ml) of semicarbazide hydrochloride, methanol and a drop of pyridine was refluxed for 40 minutes. On cooling no precipitate was formed. Next morning, after addition of water, crystal formed was collected and washed with water. It melted at 72~73.5°C, and mixed melting point with the starting ketone showed no depression. 4-Acetylfluorene gave a semicarbazone under similar condition⁹.

Attempted formation of the 2,4-dinitrophenylhydrazine of III: A mixture of 20 mg (1×10^{-4} mole) of 2,4-dinitrophenylhydrazine, 0.3 ml of 99% ethanol, two drops of 6N-hydrochloric acid and one drop of concentrated hydrochloric acid was warmed until all of the hydrazine was dissolved, and to it was added a solution of 24 mg (1.1×10^{-4} mole) of the ketone III in 0.2 ml of ethanol and reaction mixture refluxed

for few minutes and cooled. Faint turbidity was observed after one hour, but no hydrazone was formed.

Attempted detection of methyl ketone on III: To a 15% aqueous potassium hydroxide was added dropwise an aqueous iodine-iodide solution (iodine 2.5 g/20 ml) until faint yellow colour was formed, which disappeared in few minutes. To the solution mentioned above was added gently a solution of about 10 mg of the ketone in dioxane and a large amount of white inorganic precipitate was formed. After shaking, ether was added and shaken again. Ether layer was separated and evaporated to give an oil, which was boiled with aniline and aqueous potassium hydroxide in methanol but gave no smell of isonitrile. Boiling for 5 minutes before ether extraction gave also negative test.

5-Methyl-4-acetylfluorenone (IV).

a) To a solution of 74 mg of 5-methyl-4-acetylfluorene in 0.2 ml of hot acetic acid, was added in a few minutes a hot solution of 170 mg of sodium bichromate in 5 drops of water and 0.3 ml of acetic acid, and added further 0.2 ml of acetic acid and the mixture refluxed for two hours. After cooling, the mixture was poured into water, and a fine yellow precipitate was collected to give 71 mg (90%) of a product, m.p. 140~143.5°C. It was chromatographed from the same solvent to give a product, melting at 146~146.7°C. *Anal.* Found: C, 81.24; H, 5.28. Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12%.

b) Reaction of acid chloride of 5-methylfluorenone-4-carboxylic acid (I) with dimethylcadmium: Treatment of the acid chloride prepared from 0.50 g (2.1×10^{-3} mole) of I with a dimethylcadmium reagent prepared from 0.17 g (7×10^{-3} mole) of magnesium, under a similar condition in the synthesis of III mentioned above, gave an oil. Recrystallization from methanol gave 0.33 g of a solid material, melting at 90~113°C. The crude product was chromatographed on alumina and eluted with benzene-petroleum ether and recrystallized from methanol to give about 0.1 g (20%) of a product, melting at 140~144°C. Mixed melting point with pure material was 141~144°C.

Formation of the monosemicarbazone: A mixture of 11.2 mg (1.1×10^{-4} mole) of semicarbazide in 0.05 ml of water, 11.8 mg (0.5×10^{-4} mole) of the ketone IV, 0.7 ml of methanol and a drop (about 13 mg) of pyridine was heated on water bath. After

8) W. Bachmann and C. Boatner, *J. Am. Chem. Soc.*, **58**, 2097 (1936).

evaporating bulk of the methanol, a crystal formed was collected, washed with aqueous methanol and water to give a product melting at 213~214.5° (decomp.). Recrystallization from about 3 ml of ethanol gave a crystal, m.p. 215~6°C (decomp.). *Anal.* Found: N, 14.00. Calcd. for $C_{17}H_{15}N_3O_2$: N, 14.33%. The analytical datum shows that the product is a monosemicarbazone.

Attempted detection of methylketone on IV: To a solution of a few milligrams of 5-methyl-4-acetylfluorenone in two drops of dioxane, was added two drops of 10% sodium hydroxide and one drop of iodine-iodine solution (iodine 2.5 g/20 ml). Further addition of 10% sodium hydroxide and water gave a pale orange suspension. It was extracted with chloroform, and the chloroform layer was washed with water, and evaporated to give a yellow oil. Heating of the oil with aniline and potassium hydroxide in methanol for a short time gave no smell of isonitrile.

4-Methyl-5-(α -hydroxyethyl) fluorene (V).

a) Reduction with lithium aluminium hydride of II: To a ice-cooled suspension of 0.15 g (4×10^{-3} mole) of lithium aluminium hydride in absolute ether, which had been refluxed for one and a half hour with stirring, was added dropwise a solution of 0.44 g (2×10^{-3} mole) of 5-methyl-4-acetylfluorene with stirring, and the mixture refluxed for seventy minutes. After decomposition with a small amount of water, ether layer was decanted, washed with water and dried. Evaporation of the solvent yielded 0.38 g of colourless oil. All attempts to crystallize the oil were failed.

b) Reduction with sodium borohydride of III: To a solution of 0.15 g (4×10^{-3} mole) of sodium borohydride in 0.5 ml of water and 10 ml of ethanol, was added 0.72 g (0.34×10^{-4} mole) of 5-methyl-4-acetylfluorene and the mixture refluxed for two hours. After cooling, an excess of hydride was decomposed with acetic acid, bulk of the ethanol was distilled and extracted with ether. Ether layer was washed successively with dilute hydrochloric acid, dilute alkali and water and dried over anhydrous sodium sulfate. Evaporation of the ether in vacuo yielded 0.65 g of colourless oil. The oil was used for following reaction without purification.

4-Methyl-5-ethylfluorene (VI).

a) Catalytic reduction of 4-methyl-5-(α -hydroxyethyl) fluorene (V): A suspension of 0.4 g of pal-

ladium chloride on carbon corresponding to 6% palladium on carbon in acetic acid was reduced in the usual way. To the suspension was added a solution of 0.44 g of 4-methyl-5-(α -hydroxyethyl) fluorene, obtained above, in acetic acid and catalytically reduced. Ninety percent of theoretical amount of hydrogen was absorbed in fifty minutes; and the reaction mixture was shaken for additional three hours. The catalyst was filtered and the solvent was removed in vacuo to yield an oil, contaminated with a small amount of solid which dissolved in petroleum ether with difficulty. The crude oil was chromatographed on alumina and eluted with petroleum ether (b.p. 48~69°C) to give 204 mg of colourless oil as a hydrocarbon fraction. Treatment of the oil with equimolecular amount of trinitrobenzene gave a crude trinitrobenzoate, melting at 58.5~85°C, showing that the oil obtained was still crude.

b) Reduction of 4-methyl-5-ethylfluorenone (VII) with hydrazine hydrate. A mixture of 56 mg of 4-methyl-5-ethylfluorenone (m.p. 55.5~56.5°C) described in the following experiment, 0.2 ml of 80% hydrazine hydrate and 0.5 ml of diethyleneglycol in a small distilling flask was heated on an oil bath. After keeping temperature of reaction mixture at 200°C for forty minutes, a pale yellow mixture was cooled, diluted with water, and extracted with ether. Ether layer was treated in the usual way to give a neutral fraction. It was chromatographed on 1.5 g of alumina and eluted with petroleum ether (b.p. 48~69°C) to give 43 mg of colourless oil, N_D^{24} 1.6274, as a hydrocarbon fraction. The oil was used for formation of the trinitrobenzoate.

The trinitrobenzoate: Seventeen point three milligrams (0.83×10^{-4} mole) of the oil obtained above and 8.8 mg (0.41×10^{-4} mole, 0.5 equivalent) of symmetrical trinitrobenzene were dissolved in a small amount of hot ethanol, and left to stand. In a few minutes, an oily material precipitated and soon solidified. Recrystallization from ethanol gave yellow needles, melting at 62~62.5°C after sintering at 61°C. *Anal.* Found: N, 9.81. Calcd. for $C_{18}H_{16}C_6H_3N_3O_6$: N, 9.97%. In a run employing 1.7 equivalent of trinitrobenzene a slightly crude trinitrobenzoate, melting at 61~3°C after sintering at 59°C, was obtained after filtering off firstly deposited trinitrobenzene. *Anal.* Found: N, 9.77. Analytical data show that the trinitrobenzoate obtained is 1:1 adduct in both cases.

The trinitrofluorenone adduct: Prepared by Orchin's method⁹, orange crystal, m.p. 134~5°C. *Anal.* Found: C, 66.08; H, 3.96; N, 8.34. Calcd. for $C_{10}H_{10} \cdot C_{13}H_5N_3O_7$: C, 66.53; H, 4.04; N, 8.03.

The tetranitrofluorenone adduct: Prepared by 198~9°C. *Anal.* Found: C, 61.33; H, 3.49; N, 10.00. Newman and Lutz's method¹⁰, scarlet crystal, m.p. Calcd. for $C_{10}H_{10} \cdot C_{13}H_4N_4O_6$: C, 61.27; H, 3.55; N, 9.85%.

4-Methyl-5-ethylfluorenone (VII). Seventy two milligrams (0.35×10^{-3} mole) of crude 4-methyl-5-ethylfluorene obtained by catalytic reduction of 4-methyl-5-(α -hydroxyethyl)fluorene was dissolved in 0.5 ml of hot glacial acetic acid, and a solution of 180 mg (0.6×10^{-3} mole) of sodium bichromate in 0.06 ml of water and 0.25 ml of acetic acid, was added and refluxed for two hours. After cooling, the mixture was diluted with water to give a yellow oily precipitate,

which crystallized on standing and amounted to 52 mg, m.p. 51~54.5°C. It was chromatographed on alumina and eluted with benzene-petroleum ether (1:1). An oil obtained from yellow band was recrystallized from a small amount of ether to give 42 mg of yellow crystal, m.p. 56~56.15°C.

The oxime: Prepared in pyridine by Bachmann's method⁹, recrystallized from aqueous ethanol, m.p. 132~144°C. *Anal.* Found: N, 5.92. Calcd. for $C_{16}H_{15}NO$: N, 5.90%.

The 2,4-dinitrophenylhydrazone: M.p. 211.5~212.5°C. *Anal.* Found: C, 65.25, 65.40; H, 4.28, 4.08; N, 13.67. Calcd. for $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92%.

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

10) M. Newman and W. Lutz, *ibid.*, **78**, 2469 (1956).