SECTION C
Organic Chemistry

Some Substitution Reactions of 1-Methyl- and 2-Methoxy-fluorene

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A number of new compounds have been prepared by substitution of 1-methyl- and 2-methoxy-fluorene. The orientation of the products has been shown by comparison with known compounds.

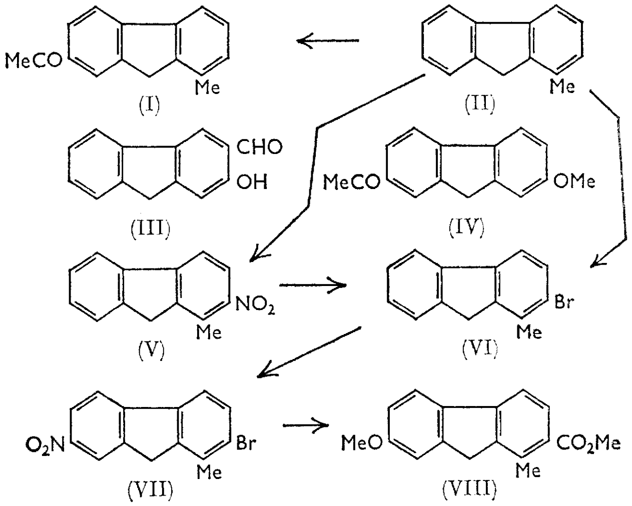
LITTLE is known about the orientation of substitution in alkylfluorenes, and, as several fluorene derivatives have now been isolated as natural products, a study has been made of some substitution reactions of 1-methylfluorene. As fluorene itself is substituted exclusively in the 2-position, it might be thought that 1-methylfluorene would give 1,2-disubstituted derivatives, unless steric hindrance is an important factor, in which case 1,7-disubstituted derivatives would be expected. The observed facts agree with this.

Friedel–Crafts acetylation of 1-methylfluorene (II) in carbon disulphide or in nitrobenzene gave a ketone with an ultraviolet spectrum very similar to that of 2-acetylfluorene, but different from that of 2-acetyl-1-methylfluorene;[1] it was therefore considered to be 7-acetyl-1-methylfluorene (I). This was confirmed by oxidation with chromic acid, which gave 8-methyl-9-oxofluorene-2-carboxylic acid.[2] This result is similar to the acetylation of toluene, which gives almost entirely the *para*-isomer.

Nitration of 1-methylfluorene gave 1-methyl-2-nitrofluorene (V), whose structure was shown by the n.m.r. spectrum, in which the methyl group produced a band at 2·83 p.p.m., a chemical shift very similar to that in *o*-nitrotoluene.[3] Reduction gave 2-amino-1-methylfluorene, which was converted by the Sandmeyer reaction into 2-bromo-1-methylfluorene (VI) and 2-cyano-1-methylfluorene, although in poor yield. Bromination of 1-methylfluorene also gave 2-bromo-1-methylfluorene, nitration of which gave 2-bromo-1-methyl-7-nitrofluorene (VII). The structure of this was shown by reduction to the corresponding amine which, on diazotisation, gave 2-bromo-7-hydroxy-1-methylfluorene in very poor yield. Debromination with hydrazine and palladised charcoal then gave 7-hydroxy-1-methylfluorene.[4]

2-Bromo-1-methylfluorene reacted with cuprous cyanide in *N*-methylpyrrolidone,[5,6] to give a good yield of 2-cyano-1-methylfluorene which, on nitration, gave 2-cyano-1-methyl-7-nitrofluorene identical with a sample produced in poor yield from 2-bromo-1-methyl-7-nitrofluorene (VII). Reduction of the nitro-group gave 7-amino-2-cyano-1-methylfluorene which, on diazotisation, gave a good yield of the phenol. 7-Methoxy-1-methylfluorene-2-carboxylic acid and its methyl ester (VIII) were prepared from the nitrile.

The acylation of 2-hydroxyfluorene was also studied, to see if it would be possible to insert a 1-substituent. Attempts to prepare an aldehyde from 2-methoxyfluorene by formylation with dimethylformamide and phosphorus oxychloride failed, but the Reimer–Tiemann reaction on the phenol gave a small yield of an aldehyde, which was converted by Wolff–Kishner reduction into a methylfluorenol. As this was not identical with 2-hydroxy-1-methylfluorene, and as the aldehyde gave an intense ferric chloride reaction indicating an *o*-hydroxy-aldehyde, it must be 2-hydroxyfluorene-3-aldehyde (III).



Friedel–Crafts acetylation of 2-methoxyfluorene in nitrobenzene gave an acetyl compound, shown to be 7-acetyl-2-methoxyfluorene (IV). Wolff–Kishner reduction of this gave 7-ethyl-2-hydroxyfluorene, which after removal of the hydroxy-group as the toluene-*p*-sulphonate[7] gave 2-ethylfluorene. Oxidation of 7-acetyl-2-methoxyfluorene with sodium hypobromite gave 7-methoxyfluorene-2-carboxylic acid.

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[1] F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 1957, 3011.

[2] T. P. C. Mulholland and G. Ward, *J. Chem. Soc.*, 1954, 4676.

[3] M. L. Jackman, " Applications of N.M.R. Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959.

[4] A. Morrison and T. P. C. Mulholland, *J. Chem. Soc.*, 1958, 2702.

[5] L. Friedmann and H. Shecheter, *J. Org. Chem.*, 1961, **26**, 2522.

[6] M. S. Newman and H. Boden, *J. Org. Chem.*, 1961, **26**, 2525.

[7] G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, 1949, S. 178.

EXPERIMENTAL

7-*Acetyl*-1-*methylfluorene* (I).—A solution of anhydrous aluminium chloride (10 g.) and acetic anhydride (4 g.) in nitrobenzene (80 ml.), cooled to 0°, was added to a cold solution of 1-methylfluorene[1] (6 g.) in nitrobenzene (60 ml.). After storing at room temperature for 24 hr. the green solution was decomposed with dilute hydrochloric acid, and the organic layer steam-distilled to remove nitrobenzene. The residue was extracted with ether; evaporation of the ether left a solid which, after filtration in benzene through an alumina column, was crystallised from methanol, to give the *product* (I) (3·8 g., 51%), m. p. 131° (Found: C, 86·7; H, 6·4. $C_{16}H_{14}O$ requires C, 86·5; H, 6·4%), $\lambda_{max.}$ 312 mμ (log ε 4·42), $\lambda_{min.}$ 250 mμ (log ε 3·39). The mother-liquors showed evidence of another substance on a chromatoplate, but this was not isolated. The *oxime* had m. p. 204—206° (from methanol) (Found: N, 5·9. $C_{16}H_{15}NO$ requires N, 5·9%).

8-*Methyl*-9-*oxofluorene*-2-*carboxylic Acid*.—7-Acetyl-1-methylfluorene (I) (500 mg.) was dissolved in acetic acid (10 ml.) and treated with sodium dichromate (4·5 g.) in acetic acid (15 ml.) and acetic anhydride (5 ml.). After refluxing for 6 hr. the solution was cooled and poured into ice–water. The precipitate was collected, washed with hot dilute sulphuric acid, and extracted with aqueous sodium carbonate. The extract was acidified and the precipitate crystallised from acetic acid, to give 8-methyl-9-oxofluorene-2-carboxylic acid (300 mg.) as bright yellow needles, m. p. 330—332° (sealed tube) (Found: C, 75·5; H, 4·2. Calc. for $C_{15}H_{10}O_3$: C, 75·6; H, 4·2%). The methyl ester, prepared with diazomethane, had m. p. 177—178°, and was identical with an authentic sample kindly supplied by Dr. Mulholland.[2]

1-*Methyl*-2-*nitrofluorene* (V).—1-Methylfluorene (5 g.) was dissolved in acetic acid (40 ml.), and concentrated nitric acid (*d* 1·42; 8 ml.) added dropwise with stirring, at 50°. After 15 min. the solution was cooled in ice, and the precipitate collected and crystallised from methanol. The *product* (V) (4·4 g., 70%) formed light yellow needles, m. p. 95° (Found: C, 74·4; H, 5·1; N, 6·4. $C_{14}H_{11}NO_2$ requires C, 74·7; H, 4·9; N, 6·2%).

2-*Amino*-1-*methylfluorene*.—(*a*) 1-Methyl-2-nitrofluorene (5·6 g.) was dissolved in ethanol and hydrogenated over palladised charcoal (0·5 g.; 5%). The solution was filtered and evaporated and the amine extracted from ether solution with dilute hydrochloric acid. The acid solution was made alkaline with sodium hydroxide, extracted with ether, the ether evaporated, and the residue crystallised from methanol. The *product* (2·9 g., 60%) formed white leaflets, m. p. 103—104° (Found: C, 86·2; H, 6·8; N, 7·1. $C_{14}H_{13}N$ requires C, 86·1; H, 6·7; N, 7·2%).

(*b*) 1-Methyl-2-nitrofluorene (8·8 g.) was dissolved in ethanol (100 ml.) and granulated tin (50 g.) was added. The solution was refluxed for 2 hr., while concentrated hydrochloric acid (50 ml.) was added slowly. The solution was filtered hot, then cooled in ice and the amine stannichloride filtered off. This was decomposed with sodium hydroxide solution, and the amine isolated with ether. Recrystallisation gave 2-amino-1-methylfluorene (5·3 g., 70%), as above. The *acetyl derivative* had m. p. 217—219° (Found: C, 80·8; H, 6·1; N, 6·2. $C_{16}H_{15}NO$ requires C, 81·0; H, 6·4; N, 5·9%).

2-*Bromo*-1-*methylfluorene* (VI).—(*a*) A solution of 2-amino-1-methylfluorene (1 g.) in water (40 ml.), acetic acid (20 ml.), and concentrated sulphuric acid (20 ml.) was heated to boiling, then cooled to 10°. A concentrated solution of sodium nitrite (0·8 g.) in water was added, followed, after stirring in ice for ½ hr., by urea (1 g.). The diazo-solution was then added to a solution of cuprous bromide in hydrobromic acid (excess) and heated to 80° for 15 min. After cooling, the solution was extracted with benzene, and the extract evaporated. The residue was filtered through alumina in light petroleum (b. p. 60—80°), then crystallised from methanol, to give the *product* (VI) (270 mg., 20%) as leaflets, m. p. 122—124° (Found: C, 65·1; H, 4·4; Br, 30·6. $C_{14}H_{11}Br$ requires C, 64·9; H, 4·3; Br, 30·8%).

(*b*) A solution of 1-methylfluorene (10 g.) and iodine (1 g.) in benzene (200 ml.) was treated with bromine (9·4 ml.) in benzene at room temperature, then refluxed for 3 hr. The solution was cooled, and washed with water and aqueous sodium hydrogen sulphite. The benzene was evaporated and the residue crystallised from methanol, to give 2-bromo-1-methylfluorene (8·8 g., 62%).

2-*Bromo*-1-*methyl*-7-*nitrofluorene* (VII).— 2-Bromo-1-methylfluorene (VI) (5 g.) in acetic acid (75 ml.) was treated at 35° with a mixture of nitric acid (*d* 1·42; 3·5 ml.) and sulphuric acid (3·5 ml.), and then warmed to 60° for 15 min. After cooling, the precipitate was collected and crystallised from benzene, to give the *product* (76—80%) as light yellow needles, m. p. 205—207° (Found: C, 55·5; H, 3·1; Br, 26·6; N, 4·7. $C_{14}H_{10}BrNO_2$ requires C, 55·3; H, 3·3; Br, 26·3; N, 4·6%).

7-*Amino*-2-*bromo*-1-*methylfluorene*.— 2-Bromo-1-methyl-7-nitrofluorene (5 g.) was dissolved in dioxan (200 ml.), and tin (15 g.) was added. Concentrated hydrochloric acid (100 ml.) was then added, and the mixture refluxed for ½ hr., filtered, diluted with water, made alkaline with sodium hydroxide, extracted with benzene, the benzene evaporated, and the residue chromatographed on alumina. Benzene–hexane mixtures eluted the *product* (2·3 g., 51%), m. p. 176—177° (Found: C, 61·2; H, 4·3; Br, 29·0; N, 5·1. $C_{14}H_{12}BrN$ requires C, 61·3; H, 4·4; Br, 29·1; N, 5·1%).

2-*Bromo*-7-*hydroxy*-1-*methylfluorene*.—The above amine (500 mg.) in water (30 ml.), acetic acid (15 ml.), and concentrated sulphuric acid (15 ml.) was heated to boiling, then cooled to 30°. A solution of sodium nitrite (150 mg.) in water was added, and the whole stirred for ½ hr. After addition of urea (200 mg.) the solution was stirred for a further ½ hr., and added to boiling water (100 ml.) containing concentrated sulphuric acid (10 ml.). The solution was refluxed for ½ hr., cooled, and extracted with ether. Evaporation of the ether gave the *product*, which crystallised from benzene as needles (140 mg., 28%), m. p. 163—164° (Found: C, 61·2; H, 4·1; Br, 28·8. $C_{14}H_{11}BrO$ requires C, 61·1; H, 4·0; Br, 29·0%).

7-*Hydroxy*-1-*methylfluorene*.—The above bromo-phenol (150 mg.), palladised charcoal (80 mg.; 10%), and hydrazine hydrate (2 ml.) were added to ethanol (20 ml.) and refluxed for 10 min. The catalyst was filtered off and the solution evaporated. Crystallisation of the residue from light petroleum (b. p. 80—100°) gave 7-hydroxy-1-methylfluorene (75 mg., 70%) as woolly needles, m. p. 166—168° undepressed by an authentic sample supplied by Dr. Mulholland[4] (Found: C, 85·6; H, 6·1. Calc. for $C_{14}H_{12}O$: C, 85·7; H, 6·2%).

2-*Cyano*-1-*methylfluorene*.—(*a*) A solution of 2-amino-1-methylfluorene (1 g.) in water (40 ml.), acetic acid (20 ml.), and concentrated sulphuric acid (20 ml.) was heated to boiling, and cooled to 10°. A solution of sodium nitrite (800 mg.) was added, followed, after stirring in ice for 1 hr., by urea (1 g.). The solution was then added dropwise to a solution of nickel sulphate (6 g.) and potassium cyanide (18 g.) in water (300 ml.) heated to 90°. After addition the mixture was kept at this temperature for 1 hr., cooled, extracted with ether, and the extract washed with dilute alkali and with water, and evaporated. Chromatography of the residue gave the *product* (250 mg., 22%), which crystallised from light petroleum (b. p. 80—100°) as woolly needles, m. p. 134—136° (Found: C, 87·6; H, 5·2; N, 7·1. $C_{15}H_{11}N$ requires C, 87·8; H, 5·4; N, 6·8%).

(*b*) 2-Bromo-1-methylfluorene (10 g.) was dissolved in *N*-methylpyrrolidone (100 ml.), and cuprous cyanide (6·3 g., freshly prepared) was added. The mixture was refluxed under nitrogen for 4 hr., and poured into a solution of ferric chloride (40 g.) and concentrated hydrochloric acid (12 ml.) in water. The solution was kept at 70° for ½ hr., and filtered. The precipitate was extracted with chloroform, and the extract washed with water and evaporated. Crystallisation from light petroleum gave 2-cyano-1-methylfluorene (7 g., 81%), identical with the sample from (*a*).

2-*Cyano*-1-*methyl*-7-*nitrofluorene*.—(*a*) 2-Cyano-1-methylfluorene (3 g.) was dissolved in acetic acid (45 ml.), and a mixture of nitric acid (*d* 1·42; 2·7 ml.) and concentrated sulphuric acid (2·7 ml.) added at 40°. The solution was warmed to 80° with stirring, and after 20 min. cooled and filtered. The precipitate was washed, dried, and crystallised from benzene, giving 2-cyano-1-methyl-7-nitrofluorene (2 g., 55%) as yellow needles, m. p. 262—264° (Found: C, 71·8; H, 4·2; N, 11·0. $C_{15}H_{10}N_2O_2$ requires C, 72·0; H, 4·0; N, 11·25%).

(*b*) 2-Bromo-1-methyl-7-nitrofluorene (1 g.) and cuprous cyanide (0·5 g.) in dimethylformamide (50 ml.) were refluxed for 4 hr. under nitrogen. After pouring into water containing ferric chloride (5 g.) and concentrated hydrochloric acid (3 ml.), the solution was kept at 60—70° for 10 min., filtered, and the dried precipitate chromatographed. Benzene–hexane eluted 2-cyano-1-methyl-7-nitrofluorene (290 mg., 35%), identical with the sample from (*a*).

7-*Amino*-2-*cyano*-1-*methylfluorene*.—2-Cyano-1-methyl-7-nitrofluorene (4 g.), palladised charcoal (800 mg.; 5%), and hydrazine hydrate (10 ml.) were refluxed in ethanol (200 ml.) for 1 hr. The solution was filtered hot and the filtrate concentrated. Filtration gave the *product* (2·5 g., 71%) as needles, m. p. 205—206° (Found: N, 12·9. $C_{15}H_{12}N_2$ requires N, 12·7%).

2-*Cyano*-7-*methoxy*-1-*methylfluorene*.— 7-Amino-2-cyano-1-methylfluorene (2·5 g.) was dissolved in a warm mixture of acetic acid (50 ml.), water (100 ml.), and concentrated sulphuric acid (50 ml.) and cooled to 30°; sodium nitrite (2 g.) was then added in a little water with stirring. The solution was stirred for ½ hr., and then urea (2 g.) was added. After filtration, the filtrate was added during ½ hr. to boiling water (750 ml.) containing concentrated sulphuric acid (75 ml.) and sodium sulphate (50 g.). The mixture was refluxed for ½ hr., cooled, and filtered, and the dried residue crystallised from acetone–methanol to give the *product* as white needles, m. p. 265—266° (Found: C, 81·3; H, 5·2. $C_{15}H_{11}NO$ requires C, 81·4; H, 5·0%). Methylation with dimethyl sulphate and alkali gave the methyl ether (1·6 g., 61%) as white needles, m. p. 167—168° (Found: C, 81·7; H, 5·5; N, 5·8. $C_{16}H_{13}NO$ requires C, 81·7; H, 5·6; N, 6·0%).

Methyl 7-*Methoxy*-1-*methylfluorene*-2-*carboxylate* (VIII).—The above methoxy-nitrile (5·5 g.) and potassium hydroxide (20 g.) in ethylene glycol (200 ml.) were refluxed for 24 hr., cooled, and poured into cold water. Acidification and ether extraction gave an acid which was esterified with diazomethane in ether–tetrahydrofuran. The *product* (VIII) crystallised from methanol as needles (3·6 g., 57%), m. p. 144—145° (Found: C, 76·3; H, 6·1. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%).

2-*Hydroxyfluorene*-3-*aldehyde* (III).—2-Hydroxyfluorene (10 g.) was dissolved in ethanol (50 ml.), and sodium hydroxide (22 g.) in water (44 ml.) added with shaking. The mixture was warmed to 60—70°, and chloroform (10 ml.) added dropwise under reflux with constant shaking. The mixture darkened, and refluxed gently. After 2 hr., excess solvent was distilled off and the residue made acid to Congo Red. After addition of water and ether, the ether layer was evaporated and the residue crystallised from light petroleum (b. p. 80—100°) and then aqueous ethanol, to give 2-hydroxyfluorene-3-aldehyde (0·5 g., 4%) as yellow needles, m. p. 143—145° (Found: C, 80·1; H, 5·0. $C_{14}H_{10}O_2$ requires C, 80·0; H, 4·8%), $\lambda_{max.}$ 210, 255 mμ (log ε 4·38, 4·52). The substance gave a deep green colour with ferric chloride.

2-*Hydroxy*-3-*methylfluorene*.—Potassium hydroxide (1 g.) was dissolved in ethylene glycol (25 ml.) by warming, and the above aldehyde (0·5 g.) and hydrazine hydrate (10 ml.) were added. After refluxing for 1 hr. at 160°, the solution was cooled and acidified. Ether extraction and crystallisation from aqueous acetic acid gave the *product* as colourless leaflets, m. p. 137—138° (Found: C, 85·6; H, 6·4. $C_{14}H_{12}O$ requires C, 85·7; H, 6·2%).

2-*Acetyl*-7-*methoxyfluorene* (IV).—Anhydrous aluminium chloride (17·2 g.), dissolved in nitrobenzene (100 ml.) and acetic anhydride (6·4 g.), was added with stirring and cooling to 2-methoxyfluorene (10 g.) in nitrobenzene (50 ml.) cooled to 5°. The solution was then allowed to attain room temperature and stored for 24 hr. After treatment with dilute hydrochloric acid, the nitrobenzene was removed by steam-distillation, and the residue extracted with ether. Evaporation and crystallisation from ethanol gave the *product* (IV) (6·25 g., 51%) as plates, m. p. 134—135° (Found: C, 80·7; H, 6·0. $C_{16}H_{14}O_2$ requires C, 80·6; H, 5·9%), $\lambda_{max.}$ 230, 327 mμ (log ε 4·16, 4·50), $\lambda_{min.}$ 220, 258 mμ (log ε 4·1, 3·29). The *oxime* formed white leaflets, m. p. 206° (from ethanol) (Found: C, 76·1; H, 6·11. $C_{16}H_{15}NO_2$ requires C, 75·9; H, 6·0%).

Use of carbon bisulphide as solvent gave a low yield (10%) of the same compound, together with a *diacetyl compound* (2%), m. p. 223° (Found: C, 76·9; H, 5·9. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·8%).

2-*Ethyl*-7-*hydroxyfluorene*.—The above acetyl compound (10 g.), diethylene glycol (120 ml.), hydrazine hydrate (50 ml.), and potassium hydroxide (8 g.) were refluxed for 4 hr. at 220°. After cooling and acidifying, the suspension was extracted with ether and the residue from evaporation of the ether boiled for ½ hr. with acetic acid (100 ml.) and hydriodic acid (35 ml.). After dilution with water the *product* was isolated with ether and crystallised from acetic acid, forming colourless leaflets (7·5 g.), m. p. 165—166° (Found: C, 85·5; H, 6·8. $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%).

2-*Ethylfluorene*.—The above phenol (7·5 g.) was dissolved in dry pyridine (30 ml.), and toluene-*p*-sulphonyl chloride (15 g.) added. The mixture was shaken until all had dissolved, then kept at 90° for 1 hr. Water was added, and the precipitate filtered off. Crystallisation from acetic acid gave the *toluene*-p-*sulphonate* of the phenol as flakes, m. p. 165°. This (5 g.) in ethanol (350 ml.) was refluxed with Raney nickel (25 g.) for 3 hr. The solution was filtered hot, and the catalyst washed with a little ethanol; evaporation gave a solid which was separated into fractions soluble and insoluble in ether. The latter was unchanged starting material, the former, recrystallised from ethanol, gave 2-ethylfluorene, white plates, m. p. 100°, identical with an authentic sample prepared from 2-acetylfluorene (Found: C, 92·8; H, 7·6. $C_{15}H_{14}$ requires C, 92·7; H, 7·3%).

Methyl 7-Hydroxyfluorene-2-carboxylate.— 7-Acetyl-2-methoxyfluorene (24 g.) was dissolved in dioxane (600 ml.) and cooled to 20°. Sodium hypobromite [from bromine (24 ml.) and sodium hydroxide (67·5 g.) in water (330 ml.)] was then added during 10 min. After keeping at 35—40° until there was no further heat evolution, the dioxan was distilled off in steam, and the residue acidified. The precipitate was filtered and esterified with diazomethane, to give *methyl 7-methoxyfluorene-2-carboxylate* (17 g., 70%) as white leaflets, m. p. 148—149° (Found: C, 75·5; H, 5·6. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·6%). Demethylation with hydrogen iodide in acetic acid, and re-esterification with methanol and hydrogen chloride, gave the corresponding *hydroxy-ester*, m. p. 229—230° (Found: C, 75·0; H, 4·9. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%).

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