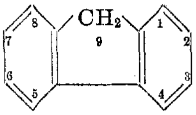
[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, THE FACULTY OF ENGINEERING, KYOTO UNIVERSITY]

THE PREPARATION OF FLUORENEACETIC ACID AND ITS DERIVATIVES

YOSHIRO OGATA, MASAKAZU INOUE, AND YASUO KITAMURA

Received March 19, 1953

In our previous paper it has been shown that 1-naphthaleneacetic acid and α-alkyl-1-naphthaleneacetic acids can be prepared by the ferric oxide-potassium bromide-catalyzed condensation of naphthalene with α-halo fatty acids (1, 2). The condensation of a similar sort has been successful with biphenyl, but difficult with benzene and most of its substituted derivatives (*e.g.*, toluene). The present paper reports the similar successful condensation of fluorene with chloroacetic acid which gave a mixture of 2- and 4-fluoreneacetic acids, the former predominating. As described in our previous reports, the positions substituted are those which the usual electrophilic reagents (*e.g.*, HNO_3) attack.



The paper also deals with some simple substitution reactions of 2-fluoreneacetic acid and several new derivatives of 2- and 4-fluoreneacetic acids. The nitration of 2-fluoreneacetic acid in acetic acid gave 7-nitro-2-fluoreneacetic acid corresponding to 2-nitrofluorene obtained by nitrating fluorene itself. Here, the position occupied by the nitro group was confirmed by reducing the nitrated product into the amino derivative and then converting the amino group into chlorine *via* the Sandmeyer reaction; the product thus obtained was identical with that of the condensation of 2-chlorofluorene with chloroacetic acid. 2-Nitrofluorene and 2-acetylfluorene could not be condensed with chloroacetic acid. The chlorination of 2-fluoreneacetic acid gave no pure product.

A patent describes that x-fluoreneacetic acid [m.p. 148° with previous softening (3, 4)] was obtained by way of the chloroacetic acid condensation without a catalyst, which, however, was less satisfactory in our hands. There have been several synthetic methods for fluoreneacetic acids, *i.e.*, 2-fluoreneacetic acid has been synthesized from the corresponding acetyl derivative by the Willgerodt reaction (5), or from the chloromethyl derivative by the replacement of chlorine by a cyano group, followed by hydrolysis (6); 9-fluoreneacetic acid by way or the malonic ester synthesis; and also 2-, 4-, and 9-fluoreneacetic acids *via* other procedures (5, 7, 8, respectively); all these methods, however, involve several tedious processes.

EXPERIMENTAL

All melting points are corrected, and all boiling points are uncorrected. Procedures described below are those by which the best yields were obtained. New compounds are indicated by *asterisks*.

2- and 4-Fluoreneacetic acids. A mixture of fluorene (80 g.) of m.p. 110–112°, chloroacetic acid (11.4 g., 0.25 equivalent), ferric oxide (0.114 g.), and potassium bromide (0.57 g.) was refluxed for 15 hours. The temperature reached 187° after 10 hours and 205° after 15 hours. The product was extracted with alkali and precipitated on acidification yielding 12.4 g. (46%) of crude acid. No condensation occurred in the absence of the catalysts under these conditions. The residue from the filtration gave 50 g. of recovered fluorene by distillation. The crude product was mixed with *ca.* 13-fold methanol and 2.5% sulfuric acid and boiled for 2 hours; the resulting methyl ester was vacuum-distilled, b.p. 200–230° (25 mm.); yield, 6 g. The ester was hydrolyzed by treatment with boiling 10% aqueous sodium hydroxide for 2 hours. After acidification of the solution, the precipitate of fluoreneacetic acid melting at *ca.* 136° weighed 5.0 g. (19%), which was found to be 2-fluoreneacetic acid admixed with a small amount of the 4-isomer. On recrystallization from acetic acid, 2-fluoreneacetic acid was obtained in the form of laminae, m.p. 189–190° [literature m.p. 186–187° (5)] which showed no depression after admixture of the authentic material prepared from 2-acetylfluorene using the Willgerodt reaction. The acetic acid mother liquor contained 4-fluoreneacetic acid in needles, m.p. 180–182° [literature m.p. 178–179° (5)], the structure of which was confirmed by the fact that its potassium salt gave on dry distillation 4-methylfluorene, m.p. 70.5–72° [literature m.p. 72.5°]. In the same way, potassium 2-fluoreneacetate gave 2-methylfluorene, m.p. 102–104° [literature m.p. 104–105°].

*Methyl 2-fluoreneacetate** was prepared from 2-fluoreneacetic acid with methanol by employing sulfuric acid as a catalyst, m.p. 83–84°.

Anal. Calc'd for $C_{16}H_{14}O_2$: C, 80.66; H, 5.92.
Found: C, 80.89; H, 5.94.

Similarly the *4-isomer** was obtained, m.p. 83–84°. The mixture m.p. of these two isomeric esters was depressed.

Anal. Found: C, 80.97; H, 5.99.

The 4-fluoreneacetic acid was converted into its amide by the treatment with phosphorus pentachloride and then with aqueous ammonia; *4-fluoreneacetamide,** m.p. 199–200° [the 2-isomer is already known (5)].

Anal. Calc'd for $C_{15}H_{13}NO$: C, 80.65; H, 5.87; N, 6.27.
Found: C, 80.54; H, 5.62; N, 6.30.

*2-Fluoreneacetonitrile.** A mixture of fluorene (80 g.), chloroacetonitrile (18.2 g., 0.5 equivalent), ferric oxide (0.122 g.), and potassium bromide (0.610 g.) was refluxed for 20 hours; the temperature rose to 172° after 10 hours and 223° after 20 hours. The reaction product was vacuum-distilled. After the recovery of unreacted fluorene (37 g.), 20.4 g. (52%) of the crude product, b.p. 220–260° (35 mm.) was obtained. It was recrystallized from ether and then acetic acid, yielding laminae of m.p. 131–132°.

Anal. Calc'd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82.
Found: C, 87.92; H, 5.28; N, 6.69.

A similar hydrolysis with 40% aqueous potassium hydroxide gave 2-fluoreneacetic acid, its m.p. and mixture m.p. with the authentic material, 187–189°.

The first crude distillate contained crystals very difficultly soluble in most organic solvents; it gave needles of m.p. 227.5–230° on recrystallization from acetic acid which does not contain nitrogen and has the empirical formula $C_{13}H_9$. The mixture with 9,9′-bifluorenyl showed no depression of melting point.

Anal. Calc'd for $C_{26}H_{18}$: C, 94.51; H, 5.49.
Found: C, 93.39; H, 5.76.

*7-Nitro-2-fluoreneacetic acid**. 2-Fluoreneacetic acid (20 g., 0.09 mole) was dissolved in acetic acid (46 cc.) at 70–80° and cooled to 50°. Into the solution was added with stirring 21 cc. (0.3 mole) of conc'd nitric acid (*sp. gr.* 1.41) during 30 minutes. The mixture was kept under agitation at 70–80° for one hour. After allowing to stand overnight, the yellow precipitate was ice-cooled and filtered from the solution. Crude *7-nitro-2-fluoreneacetic acid,* m.p. *ca.* 213°, was obtained in 66% yield (15.7 g.). After recrystallization from acetic acid, the acid in the form of light yellow needles melted at 223–225° (open) and 220–222° (block), with *ca.* 30% loss on recrystallization. Titration gave a molecular weight of 265; Calc'd for the monobasic acid, $C_{15}H_{11}NO_4$: 269.

Anal. Calc'd for $C_{15}H_{11}NO_4$: C, 66.94; H, 4.12; N, 5.20.
Found: C, 66.72; H, 4.42; N, 5.54.

*7-Amino-2-fluoreneacetic acid**. A mixture of 7-nitro-2-fluoreneacetic acid (5 g.), tin foil (5 g.), and conc'd hydrochloric acid (50 cc.) was gently refluxed for 10 hours. During the reaction, tin foil (12 g.) together with hydrochloric acid (80 cc.) was added in several portions to the mixture. After being separated from the residual tin foil by the hot filtration, the solution was concentrated and cooled to the point of deposition of crystals. The crude *7-amino-2-fluoreneacetic acid hydrochloride* weighed 3.7 g. The pure product was obtained in the form of laminae on recrystallization from dil. hydrochloric acid (conc'd $HCl:H_2O$ = 1:16), m.p. 275–280° (dec., block), 277–281° (dec., open). The recrystallization resulted in about a 50% loss of the material.

Anal. Calc'd for $C_{15}H_{14}ClNO_2$: C, 65.3; H, 5.1; N, 5.1.
Found: C, 64.4; H, 5.8; N, 5.1.

Diazotized 7-amino-2-fluoreneacetic acid produced dyestuffs when coupled with 1-naphthol (violet), 2-naphthol (red), naphthol AS (reddish violet), H-acid (deep violet), G-acid (brown), R-acid (light red), 1-naphthylamine (light brown), and diphenylamine (brown).

The potassium salt of this amino acid was dry distilled. The reddish brown oily product, *2-methyl-7-aminofluorene*,* was obtained, which on several recrystallizations from methanol-hydrochloric acid gave its *hydrochloride* in the form of laminae, m.p. 310–313° (block), 312–314° (open).

Anal. Calc'd for $C_{14}H_{14}ClN$: C, 72.56; H, 6.1.
Found: C, 72.00; H, 6.1.

7-Chloro-2-fluoreneacetic acid. From 7-amino-2-fluoreneacetic acid by the Sandmeyer reaction.* 7-Amino-2-fluoreneacetic acid hydrochloride (5 g.) was dissolved in aqueous hydrochloric acid (5 cc. of conc'd acid in 80 cc. of water), cooled, and then diazotized with sufficient stirring by a conc'd solution of sodium nitrite (1.25 g.). The diazo solution was run at 40–50° into a cuprous chloride solution prepared from crystalline cupric sulfate (5.5 g.), sodium chloride (1.8 g.), sodium bisulfite (0.9 g.), and conc'd hydrochloric acid in the usual way (9). The solution was then refluxed for 1.5–2 hours, the precipitate being collected by filtration. The crude *7-chloro-2-fluoreneacetic acid* melted at 140–145°. The yield was 2.3 g. The pure product was obtained in the form of light yellow powder on recrystallization from ether, m.p. 167–169°. Titration gave molecular weight of 253.3 (Calc'd for $C_{15}H_{11}ClO_2$: 258.8).

Anal. Calc'd for $C_{15}H_{11}ClO_2$: C, 69.65; H, 4.27.
Found: C, 70.40; H, 4.68.

From 2-chlorofluorene by condensation with chloroacetic acid. 2-Chlorofluorene was prepared by the chlorination of fluorene with sulfuryl chloride in ether at 30°, m.p. 96° (10). The reaction of fluorene with chlorine (11) gave a less pure product in our own hands. A mixture of 2-chlorofluorene (30 g., 0.15 mole), chloroacetic acid (14.3 g., 0.15 mole), ferric oxide (0.05 g.), and potassium bromide (0.24 g.) was heated under reflux for 20 hours; the temperature reached to 195° after 10 hours and 215° after 20 hours. The reaction product contained a large amount of tarry matter and it was extracted with sodium hydroxide and worked up as already described (12). Upon several crystallizations from acetic acid, the pure acid melted at 168–170°. The identification of the two chlorofluoreneacetic acids was established by a mixture melting point depression.

Acknowledgment. The authors wish to thank the Yawata Iron Works for their gift of fluorene, to Mr. Masaya Okano for his suggestions, and to Mr. Kei-ichi Matsuda for his assistance.

SUMMARY

1. The ferric oxide-potassium bromide-catalyzed condensations of chloroacetic acid and chloroacetonitrile with fluorene have been studied. 2- and 4-Fluoreneacetic acids and 2-fluoreneacetonitrile have been synthesized.

2. The following new compounds have been synthesized from 2- and 4-fluoreneacetic acids using well-known procedures: methyl 2-fluoreneacetate and its 4-isomer, 4-fluoreneacetamide, 7-nitro-, 7-amino-, and 7-chloro-2-fluoreneacetic acids, and 2-methyl-7-aminofluorene hydrochloride.

YOSHIDA, KYOTO, JAPAN.

REFERENCES

(1) OGATA, ISHIGURO, AND KITAMURA, *J. Org. Chem.*, **16**, 239 (1951).
(2) OGATA, OKANO, AND KITAMURA, *J. Org. Chem.*, **16**, 1588 (1951).
(3) WOLFRAM, SCHÖRING, AND HAUSDÖRFER to the General Aniline Works, U. S. Patent 1,951,686 (March 1934) [*Chem. Abstr.*, **28**, 3423 (1934)].
(4) WOLFRAM, SCHÖRING, AND HAUSDÖRFER to I. G. Farbenind, German Patent 562,391 (February 1929) [*Frdl.*, **19**, 779 (1934)].
(5) BACHMANN AND SHEEHAN, *J. Am. Chem. Soc.*, **62**, 2687 (1940).
(6) COOK AND STEPHENSON, *J. Chem. Soc.*, 842 (1949).
(7) VON BRAUN AND ENGEL, *Ber.*, **57**, 191 (1924).
(8) MAYER, *Ber.*, **46**, 2586 (1913); WISLICENUS AND EBLE, *Ber.*, **50**, 261 (1917); SIEGLITZ AND JASSOY, *Ber.*, **54**, 2133 (1921).
(9) HARTMAN AND BRETHEN, *Org. Syntheses*, Coll. Vol. I, 2nd Ed., 162 (1941).
(10) STREITWIESER, E. *Am. Chem. Soc.*, **66**, 2127 (1944).
(11) BUFFLE, *Helv. Chim. Acta*, **15**, 1483 (1932).
(12) OGATA AND ISHIGURO, *J. Am. Chem. Soc.*, **72**, 4302 (1950).