TABLE II

FLUOROALDEHYDES

Name	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
4-Dimethylamino-2-fluorobenzaldehyde	62.9–64.5°	74.3	$C_9H_{10}FNO$	64.66	6.03	64.31	5.83[a]
						64.46	5.83
4-Dimethylamino-2,5-difluorobenzaldehyde	60.8–62.0°	17.3	$C_9H_9F_2NO$	58.37	4.90	58.43	5.00[a]
						58.45	5.20

[a] Analysis by Weiler and Strauss.

recrystallizing the residue repeatedly from ethanol, and subliming in vacuum, m.p. 145.7–147.0°.

Anal. Calcd. for $C_7H_5BrClNO$: C, 35.85; H, 2.15. Found: C, 35.63, 35.48; H, 2.23, 2.33.[8]

CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN.

Synthesis of *dl*-β-(1-Fluorenyl)alanine

D. C. MORRISON

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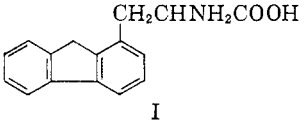
In continuation of work begun with the synthesis of *dl*-β-(2-fluorenyl)alanine[1] the corresponding 1-fluorenyl isomer has been prepared. The substance I may be of interest in cancer chemotherapy and as an aromatic amino acid.



I

It was obtained from fluorene-1-carboxylic acid[2] II as starting material by a route similar to that used for the 2-isomer. Reduction of the 1-methyl ester by lithium aluminum hydride gave the 1-carbinol[3] III, which was converted to the corresponding bromide[3] with phosphorus tribromide. The bromide was employed to alkylate the sodium derivative of diethyl acetamidomalonate, and the intermediate ester was hydrolyzed by hydrochloric acid to the amino acid hydrochloride. This salt, when dissolved in dilute alkali and acidified with acetic acid gave the free amino acid. The hydrochloride serves to characterize the compound.

The amino acid was a very sparingly soluble crystalline powder, similar in most physical properties to the 2-isomer. The melting point and that of the hydrochloride were not very sharp as is usually observed with this type of compound.

The infrared spectrum of the free amino acid in a potassium bromide disk showed a wide multicomponent band between 3100–2900 cm.$^{-1}$, probably due to C—H stretching and NH_3^+ stretching. A series of peaks at 1640 (sh), 1613, 1584, 1486, and 1410 cm.$^{-1}$ may be ascribed to C=C stretching, NH_3^+ deformation, and carboxylate ion vibrations but single assignments would be difficult. A very strong band at 759 cm.$^{-1}$ is attributable to C—H out of plane bending.

(1) D. C. Morrison, *J. Org. Chem.*, **24**, 463 (1959).
(2) D. C. Morrison, *J. Org. Chem.*, **23**, 1772 (1958).
(3) L. A. Pinck and G. E. Hilbert, *J. Am. Chem. Soc.*, **68**, 752 (1946).

EXPERIMENTAL

Melting points are uncorrected and were taken on a Fisher-Johns block.

1-Hydroxymethylfluorene. Methyl fluorene-1-carboxylate was prepared by conventional esterification with methanol and sulfuric acid. It was distilled from a small still at 1 mm. pressure and recrystallized from acetone-water. The greater solubility of the ester in organic solvents was an advantage over use of the free acid in reductions. The methyl ester (8.4 g. or 0.038 mole) was treated with lithium aluminum hydride as described for the 2-isomer[1] and gave a nearly theoretical yield (7.4 g.) of crude fluorenyl-carbinol. This melted at 137–146°, and after several recrystallizations from ether–petroleum ether (b.p. 30–60°) had a melting point of 146.5–147.5°. Pinck and Hilbert[3] give 148° corr. The carbinol could also be distilled at 1 mm. to aid in its purification.

1-Bromomethylfluorene. This was prepared by a process similar to that used for the 2-isomer[1] and was obtained in nearly theoretical yield. If insufficient phosphorus tribromide is used, some starting material may be recovered unchanged. The crude product melted at 97–102° and when recrystallized from ether and petroleum ether, this was raised to 100–101.5° with previous sintering; lit.[3] m.p. 104° corr.

Diethyl (1-fluorenylmethyl)acetamidomalonate. A solution of 0.92 g. (0.04 mole) of sodium in absolute ethyl alcohol was treated with 8.7 g. (0.04 mole) of diethyl acetamidomalonate and warmed for solution. Now 10.4 g. (0.04 mole) of the bromide (m.p. 97–102°) was added and the mixture refluxed 16 hr. If variations from the theoretical amounts are used, the product cannot be purified easily. Most of the ethanol was distilled and 3 ml. of acetic acid and an excess of water were added. After leaving overnight on ice, the solid product was filtered, washed with water, and dried. It weighed 15 g. or 94.9%. The ester could be recrystallized from aqueous acetone with difficulty. Slow crystallizations from clear solutions, taking center fractions, were carried out twelve times to obtain a pure product. This was a cream-white powder, m.p. 120–121°.

Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.87; H, 6.33. Found: C, 69.91; H, 6.19.

DL-β-*(1-Fluorenyl)alanine hydrochloride.* A solution of 14.8 g. (0.0375 mole) of the crude ester in 150 ml. of glacial acetic acid was heated to boiling under reflux. While boiling, a mixture of 60 ml. of concd. hydrochloric acid and 10 ml. of water was added and reflux continued for 48 hr. Most of the solvent was now distilled and the residue extracted repeatedly with boiling 2*N* hydrochloric acid until nothing further was removed. The extracts were filtered at 90° or higher and the filtrates cooled to obtain the product. This was filtered and the filtrates concentrated to a small volume for a second crop. The combined weight of hydrochloride was 9.3 g. or 85.8%. The hydrochloride could be

recrystallized from hot dilute hydrochloric acid but it was best to cause slow deposition of the salt from the dilute acid at room temperature on standing. After several recrystallizations in this way, it was further recrystallized from ethanol-toluene and then formed a nearly white crystalline powder. The best material, on heating, began to turn orange at 210–215° with melting at 228–234° to an orange-brown melt.

Anal. Calcd. for $C_{16}H_{16}NO_2Cl$: C, 66.32; H, 5.53. Found: C, 66.69; H, 5.80.

DL-*β*-(*1-Fluorenyl*)*alanine.* The hydrochloride could be converted to the free amino acid by extraction with ammonium hydroxide and acidification with acetic acid. This tended to form a pink product, especially if heated. It was found preferable to acidify a very dilute solution of the hydrochloride in dilute potassium hydroxide with acetic acid so that the amino acid slowly deposited at room temperature. In this way, a nearly white crystalline product was formed. On heating, the best sample began to turn orange at 210–212° and melted 221–230° to an orange-brown melt.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.93. Found: C, 76.04; H, 5.96.

Reaction with ninhydrin. The amino acid was suspended in dilute acetic acid and treated with an excess of ninhydrin and heated. A greenish-gray solution was formed at first which became dark blue-gray on further heating. On boiling a few minutes, a purple solution was produced with dark blue-gray particles (from undissolved amino acid) in suspension.

DEPT. OF PHYSIOLOGICAL CHEMISTRY
UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE
BERKELEY, CALIF.

Preparation of *N*-Substituted Glycines. II. *N*-(3,5-Dinitro-2-thienyl)glycine[1,2a]

JACK M. TIEN AND I. MOYER HUNSBERGER[2b]

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Our interest in *N*-heteroaryl derivatives of the sydnone ring system[3] led us to attempt the preparation of an *N*-thienylsydnone. As no *N*-thienylglycines have been reported in the literature, we first attempted to prepare *N*-2-thienylglycine by condensation of 2-chlorothiophene with glycine ethyl ester hydrochloride (I); however, only unchanged chlorothiophene was isolated. The more reactive 2-bromo-5-nitrothiophene (II) also failed to condense with I. Finally, the hitherto unreported 2-bromo-3,5-dinitrothiophene (III) was prepared in high yield by nitration of 2-bromo-5-nitrothiophene with mixed acid at low temperature. After considerable difficulty the condensation of III with I was effected by heating in absolute ethanol containing a rather carefully regulated amount of zinc oxide. In this way the ethyl ester (IV) of *N*-(3,5-dinitro-2-thienyl)glycine, m.p. 125–126°, was obtained in good yield. Acid hydrolysis of IV then afforded the desired *N*-(3,5-dinitro-2-thienyl)glycine (V). Esterification of V regenerated IV.

All attempts to nitrosate both the glycine (V) and its ethyl ester (IV) were unsuccessful; methods specifically designed for nitrosating weakly basic amines gave only unchanged starting material. As 3,5-dinitro-2-thienol[4] is a much stronger acid than 2,4-dinitrophenol, it seems likely that IV and V also are weaker bases than the corresponding benzene derivatives. Apparently, two nitro groups on the thiophene ring exert effects comparable to three nitro groups on the benzene ring. In this connection it is noteworthy that V separated as the free base from aqueous hydrochloric acid and that IV did not form a hydrochloride salt in absolute ethanol saturated with dry hydrogen chloride.

Further work in this series was abandoned because of the extremely potent vesicant action of both II and III (see Experimental).

EXPERIMENTAL[5]

2-Bromo-3,5-dinitrothiophene (III).[6] Concentrated sulfuric acid (45 ml.) and 60 ml. of yellow fuming nitric acid (sp. gr. 1.49–1.50)[7] were mixed at −5°. The mixed acid was kept at −5° (ice-salt bath) while 14.6 g. (0.070 mole) of II[8] was added portionwise (stirring) during 25 min. After about 10 min. a pasty mass had formed. The ice-salt bath was replaced by a water bath, and stirring was continued for another 25 min. The yellow slurry was poured onto chipped ice to yield 17 g. (96%) of III as a pale yellow crystalline powder, m.p. 135–136°. Recrystallization from hot ethanol afforded colorless plates of unchanged m.p.

Anal. Calcd. for $C_4HN_2O_4BrS$: Br, 31.59; S, 12.67. Found: Br, 31.51; S, 12.53.

This compound was very soluble in acetone, chloroform, dioxane, and petroleum ether; it was soluble in ether but insoluble in benzene, water, and concentrated or dilute hydrochloric acid.

Ethyl ester (IV) *of N-(3,5-dinitro-2-thienyl)glycine.* A hot solution of 6.3 g. (0.045 mole) of I in 450 ml. of absolute ethanol was treated with 11.0 g. (0.0435 mole) of III and 1.40 g. (0.0172 mole) of zinc oxide. The reagents were added alternately and in about six equal portions, a given portion not being added until the preceding one had dissolved. The yellow solution was refluxed in a hot water bath for 2 hr. On cooling, the solution deposited 9.80 g. (82%) of crude IV as yellow to brown needles. Recrystallization from hot

(1) Paper I: J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.* **77**, 6696 (1955).

(2) (a) Supported, in part, by a research grant (CY-2962) from the National Cancer Institute of the Public Health Service and by the U. S. Air Force under Contract No. AF 18(603)-127, monitored by the Air Force Office of Scientific Research of the Air Research and Development Command. Reproduction in whole or in part is permitted for any purpose of the United States government. (b) To whom all inquiries should be sent: Department of Chemistry, University of Massachusetts, Amherst, Mass.

(3) J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.*, **77**, 6604 (1955).

(4) C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **74**, 2965 (1952).

(5) All combustion analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(6) This procedure is similar to that used[4] for nitrating 2-chloro-5-nitrothiophene.

(7) Red fuming nitric acid produced virtually identical results.

(8) V. S. Babasinian, *J. Am. Chem. Soc.* **57**, 1764 (1935).