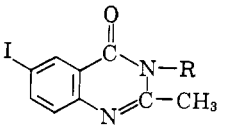
TABLE I
2-METHYL-3-R_1-6-IODO-4-QUINAZOLONE



R_1	M.p., °C.[b]	Yield, %	Formula	Crystn. solvent	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
Phenyl[a]	151.2 (151–152)	50	$C_{15}H_{11}IN_2O$	EtOH	49.7	3.03	7.03	49.3	3.0	7.4
Benzyl	(121–123)	75	$C_{16}H_{13}IN_2O$	EtOH	51.06	3.03	7.4	51.0	3.2	7.8
o-Tolyl[a]	137.8–139.6 (142–144)	70	$C_{16}H_{13}IN_2O$	EtOH–H_2O	51.06	3.4	7.4	51.1	3.6	7.5
m-Tolyl[a]	177–179 (179–181)	60	$C_{16}H_{13}IN_2O$	EtOH–H_2O	51.06	3.4	7.4	50.9	3.2	7.3
o-Anisyl[a]	177–179 (178–180)	50	$C_{16}H_{13}IN_2O_2$	EtOH	48.98	3.31	7.13	48.64	3.01	7.2
m-Anisyl	175–177	45	$C_{16}H_{13}IN_2O_2$	EtOH	48.98	3.31	7.13	48.73	3.45	7.4
α-Naphthyl	155–157	55	$C_{19}H_{14}IN_2O$	EtOH	55.34	3.16	6.7	55.64	3.53	6.5
β-Naphthyl	253.5	55	$C_{19}H_{14}IN_2O$	EtOH	55.34	3.16	6.7	55.85	3.18	6.2
o-Aminophenyl	>290	30	$C_{15}H_{13}IN_3O$	EtOH–AcOH	47.8	3.18	11.1	47.3	3.09	11.45
p-Aminophenyl	>290	40	$C_{15}H_{13}IN_3O$	EtOH–AcOH	47.8	3.18	11.1	47.5	3.23	11.0
Isopropyl	177–178	40	$C_{12}H_{13}IN_2O$	EtOH	43.9	4.0	8.5	43.6	4.4	8.4
2-Hydroxyethyl	177–179	40	$C_{11}H_{11}IN_2O_2$	EtOH	40.00	3.8	8.4	39.8	3.7	8.9
n-Butyl	114–116	45	$C_{13}H_{15}IN_2O$	EtOH	43.9	4.00	8.5	43.5	3.9	8.2
Anilino	217.5	35	$C_{15}H_{12}IN_3O$	AcOH–C_6H_6	47.7	3.1	11.1	47.5	3.0	11.5
p-Nitrophenyl[a]	207–209 (209–210)	60	$C_{15}H_{11}IN_3O_3$	EtOH	44.2	2.4	10.3	44.00	2.7	10.2
2,4-Dinitroanilino	171–172	30	$C_{15}H_{10}IN_5O_5$	C_6H_6	38.5	2.71	14.9	38.2	2.5	14.8
2-Pyridyl	166–168	70	$C_{14}H_{12}IN_4O$	EtOH	46.3	2.7	11.56	46.11	2.5	11.55
3-Methyl-2-pyridyl	159–161	70	$C_{15}H_{14}IN_4O$	EtOH	49.5	3.3	7.7	49.3	3.00	7.6

[a] These compounds have been synthesized earlier by a different synthetic method. [b] Figures in parentheses are the melting points reported in the literature.

Derivatives of Fluorene. XX.[1a,b] Fluorofluorenes. V. New Difluoro-2-acetamidofluorenes for the Study of Carcinogenic Mechanisms

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Six monofluoro-2-acetamidofluorenes (2-AAF)[2] and the first two (1,7 and 3,7) difluoro-2-AAF have been reported.[3] Results of testing of some of these substances, by Miller and Miller of the McArdle Memorial Laboratory, and reasons for testing these substances have been published.[4]

We here describe preparation of three new (4,7, 5,7, and 6,8) difluoro-2-AAF and related compounds. The first two have fluorine in the 7-position which markedly enhances liver carcinogenicity of 2-AAF[5] perhaps by blocking a detoxification site, perhaps also by altering the potency of the N-hydroxy metabolite which is more carcinogenic than the AAF itself.[6]

Since some polychlorofluorenes show antitumor effects, a few of the present compounds were tested by the CCNSC, but the results indicate that none of them has cytotoxic effects.

Experimental[7]

2,5-Difluorofluorenone.—To 42.6 g. (0.2 mole) of 5-fluoro-9-oxo-2-fluorenamine[2b] in 100 ml. of dimethyl sulfoxide,[8] 200 ml. of 48% fluoroboric acid was added with stirring. After cooling to 0°, a saturated solution of 21 g. (0.3 mole) of $NaNO_2$ was added slowly. After stirring for 30 min., the salt was filtered off, washed with 20 ml. of 5% fluoroboric acid, 20 ml. of methanol, and 20 ml. of ether, and dried giving 58 g. (93%) of salt, dec pt. 180°. This was decomposed in 500 ml. of boiling *o*-dichlorobenzene which was boiled down to near dryness, 100 ml. of benzene was added, and the mixture was filtered. Upon cooling, a precipitate was filtered off, giving 31 g. (72%) of product, m.p. 142–144°. Recrystallization from ethanol raised the melting point to 146–147°. An analytical sample was prepared by sublimation at 140° (1 mm.); m.p. 147–147.5°; ν_{max} 1721 (keto C=O), 1274, 1233 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_6F_2O$: C, 72.22; H, 2.80; F, 17.58. Found: C, 72.44; H, 2.80; F, 17.22.

4,7-Difluoro-2-nitrofluorenone.—To 60 ml. of HNO_3 (90%), 31 g. (0.144 mole) of 2,5-difluorofluorenone was added in portions with stirring and cooling (below 30°). The mixture was removed from the ice bath, and with continued stirring, the temperature

(1) (a) This work was supported in part by a grant (CA-01744) from the National Cancer Institute and, in part, by a Career Development Award 5K3-GM-14,991 to T. L. F. (b) For Part XIX see T. L. Fletcher, M. J. Namkung, J. R. Dice, and S. K. Schaefer, *J. Med. Chem.*, **8**, 347 (1965). (c) To whom requests for reprints should be addressed.

(2) (a) T. L. Fletcher, W. H. Wetzel, M. J. Namkung, and H. L. Pan, *J. Am. Chem. Soc.*, **81**, 1092 (1959); (b) T. L. Fletcher, M. J. Namkung, H. L. Pan, and W. H. Wetzel, *J. Org. Chem.*, **25**, 996 (1960); (c) T. L. Fletcher, M. J. Namkung, W. H. Wetzel, and H. L. Pan, *ibid.*, **25**, 1342 (1960).

(3) M. J. Namkung and T. L. Fletcher, *ibid.*, **26**, 2243 (1961).

(4) E. C. Miller, T. L. Fletcher, A. Margreth, and J. A. Miller, *Cancer Res.*, **22**, 1002 (1962).

(5) J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *ibid.*, **15**, 188 (1955).

(6) E. C. Miller, J. A. Miller, and H. A. Hartmann, *ibid.*, **21**, 815 (1961).

(7) Melting points, except those above 300°, are corrected to standards and were taken on a Fisher-Johns block. The infrared spectra were taken in KBr disks with a Beckman IR-5 at a concentration of *ca.* 1.5 mg./300 mg. of KBr. Band assignments for C–F stretching are tentative and a continuation of earlier data.[2c] Analyses were run by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by A. Bernhardt, Mülheim (Ruhr), Germany.

(8) T. L. Fletcher and M. J. Namkung, *Chem. Ind.* (London), 179 (1961).

rose to 35° and a precipitate formed. It was stirred into 500 ml. of ice water and the product was filtered off and dried. Crystallization from toluene yielded 32 g. (86%), m.p. 207–208°. Recrystallization from alcohol gave m.p. 207–208°; ν_{max} 1721 (keto C=O), 1264, 1235 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_5F_2NO_3$: C, 59.78; H, 1.93; N, 5.36. Found: C, 60.01; H, 2.17; N, 5.49.

4,7-Difluoro-9-oxo-2-fluorenamine.—A mixture of 26.1 g. (0.1 mole) of 2-nitro-4,7-difluorofluorenone, 175 ml. of concentrated HCl, 90 ml. of ethanol, and 130 g. (0.57 mole) of $SnCl_2 \cdot 2H_2O$ was boiled for 15 min. A vigorous reaction took place, followed by deposition of yellow crystals. When the mixture was at room temperature, the precipitate was filtered off and washed with 20 ml. of dilute HCl and suspended in 50 ml. of water which was made alkaline with NH OH. The precipitate was filtered off, washed, dried, and dissolved in 2 l. of boiling toluene. Inorganic material was filtered off, and the filtrate was concentrated to 600 ml. and cooled. Dark purple crystals came out; 20.2 g. (86%); m.p. 234–235°; ν_{max} 1709 (keto C=O), 1271, 1248 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_7F_2NO$: C, 67.55; H, 3.05; N, 6.06. Found: C, 67.99; H, 3.09; N, 6.13.

N-2-(4,7-Difluoro-9-oxofluorenyl)acetamide.—Acetylation gave a product which was recrystallized from alcohol; m.p. 275–276°; ν_{max} 1724 (keto C=O), 1269, 1235 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_9F_2NO_2$: C, 65.93; H, 3.32; N, 5.13. Found: C, 65.93; H, 3.61; N, 5.12.

4,7-Difluoro-2-fluorenamine.—A mixture of 20 g. (0.0865 mole) of 4,7-difluoro-9-oxo-2-fluorenamine, 50 g. (1.6 moles) of red P, 60 ml. of 47% HI, and 500 ml. of glacial acetic acid refluxed for 48 hr. then was boiled to near dryness, 500 ml. of boiling water was added, and the mixture was filtered. Upon addition of NH_4OH a precipitate formed which was filtered off, washed, and dried, giving 16.8 g. (89%), m.p. 120–121°. Recrystallization from alcohol gave m.p. 119.5–121°; ν_{max} 1280, 1239 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_9F_2N$: N, 6.45. Found: N, 6.48.

Single-Step Reduction of 4,7-Difluoro-2-nitrofluorenone to the Fluorenamine.—Reduction of 4 g. (0.015 mole) of 4,7-difluoro-2-nitrofluorenone with 10 g. of red P and 12 ml. of 47% HI in 100 ml. of glacial acetic acid as described below for the 5,7-difluoro-2-nitro isomer, gave 2.9 g. (87.5%), m.p. 119–121°. A mixture melting point with the product obtained above showed no depression.

N-2-(4,7-Difluorofluorenyl)acetamide.—Acetylation gave a quantitative yield. An analytical sample was obtained after two recrystallizations from alcohol; m.p. 207–208°; ν_{max} 1272, 1252 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{11}F_2NO$: C, 69.49; H, 4.28; F, 14.66; N, 5.40. Found: C 69.35; H, 4.48; F, 14.38; N, 5.25.

2,4,7-Trifluorofluorenone.—Diazotization of 4,7-difluoro-9-oxo-2-fluorenamine was carried out in tetrahydrofuran[8] and the salt (dec. pt. *ca.* 90°) decomposed in boiling toluene, giving 73% of product, m.p. 156–159°. Recrystallization from alcohol and sublimation at 160° (1 mm.) gave an analytical sample: m.p. 162.5°–163°; ν_{max} 1721 (keto C=O), 1285, 1235, 1116 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_5F_3O$: C, 66.67; H, 2.15; F, 24.34. Found: C, 66.55; H, 2.29; F, 24.63 (see alternate synthesis below).

2,4-Difluoro-9-oxofluorene (Improved Synthesis).—An Ullmann synthesis was run using 90 g. (0.376 mole) of 2,4-difluoroiodobenzene (from 2,4-difluoroaniline), $n^{22}D$ 1.5585 (lit.[9] $n^{20}D$ 1.5574), and 293 g. (1.36 moles) of methyl *o*-bromobenzoate with 235 g. of powdered copper from Metals Disintegrating Co., Grade 450A, added in three portions at 0.5-hr. intervals.[10] The temperature was kept at 215° and vigorous stirring was maintained for a total of 4 hr. After the usual extractions, hydrolysis and cyclodehydration, 49 g. (60%) of the crude difluorofluorenone was obtained. It was taken up in acetone (Darco) and filtered, and the acetone was evaporated on the steam bath. It was then recrystallized from ethanol giving 30 g. of product, m.p. 140–142°. A small sample, after sublimation and recrystallization from methanol, gave m.p. 145–145.5°. A mixture melting point with a sample prepared earlier in very small yield[2e] [ν_{max} 1718 (keto C=O), 1307, 1112 (C–F stretching) cm.$^{-1}$] showed no depression. Only 4.4 g. of neutral fraction was obtained in this synthesis, presumably **2,4,2′,4′-tetrafluorobiphenyl**.

2,4-Difluoro-7-nitro-9-oxofluorene. A.—To 30 ml. of HNO_3, 15 g. (0.07 mole) of 2,4-difluorofluorenone was added in portions with stirring. The temperature rose to 70° with evolution of fumes. The mixture was stirred for 10 min. and poured into 100 ml. of ice water. The precipitate was filtered off, washed, and dried, giving 17 g. (93.5%), m.p. 195–199°. Recrystallization from benzene (Darco) gave 13.1 g. (72%); m.p. 202–202.5°; ν_{max} 1721 (keto C=O), 1290, 1124 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_5F_2NO_3$: C, 59.78; H, 1.93; F, 14.55; N, 5.36. Found: C, 59.92; H, 1.96; F, 14.41; N, 5.15.

B.—An Ullmann procedure,[10] as described, using 14 g. (0.0585 mole) of 2,4-difluoroiodobenzene and 27 g. (0.104 mole) of methyl 2-bromo-4-nitrobenzoate with 24 g. of powdered copper, gave 0.7 g. (4.6%) of product, m.p. 198–201°. Two recrystallizations from benzene gave m.p. 201–202°. A mixture melting point with the preceding product showed no depression.

5,7-Difluoro-9-oxo-2-fluorenamine.—Reduction of 5,7-difluoro-2-nitrofluorenone with $SnCl_2 \cdot 2H_2O$ in HCl gave 88% of the amine after recrystallization from toluene, m.p. 212–212.5°. An analytical sample was obtained by one more recrystallization: m.p. 212–212.5°; ν_{max} 1715 (keto C=O), 1290, 1111 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_7F_2NO$: C, 67.55; H, 3.05; N, 6.06. Found: C, 67.71; H, 3.05; N, 6.01.

2,4,7-Trifluorofluorenone.—The preceding compound (1 g.) was diazotized in 20 ml. of fluoroboric acid (48%) with an aqueous solution of 0.5 g. of $NaNO_2$ in the presence of 10 ml. of dimethyl sulfoxide[8] at 0°. The salt (dec. pt. *ca.* 160°) was decomposed *in vacuo* in a bath (160–170°) to yield 0.6 g. (60%), m.p. 161–162°. Crystallization from alcohol raised the melting point to 161.5–162.5°. A mixture, with the compound described above from 4,7-difluoro-9-oxo-2-fluorenamine, melted at 161.5–163°. The infrared spectra were identical.

N-2-(5,7-Difluoro-9-oxofluorenyl)acetamide.—Acetylation and recrystallization from toluene gave m.p. 252–252.5°; ν_{max} 1724 (keto C=O), 1292, 1105 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_9F_2NO_2$: N, 5.13. Found: N, 5.11.

5,7-Difluoro-2-fluorenamine. A. Single-Step Reduction of 5,7-Difluoro-2-nitrofluorenone. 1.—A mixture of 7.3 g. (0.028 mole) of 5,7-difluoro-2-nitrofluorenone, 100 ml. of diethylene glycol, and 50 ml. of 85% hydrazine hydrate was refluxed for 1 hr. and then boiled without condenser until the temperature of the solution reached 205°. Refluxing was then continued for 1.5 hr. The reaction mixture was cooled and poured into 400 ml. of water. The precipitate was filtered off, washed, and dried, giving 6.1 g. (100%) of material, m.p. 75–80°. Recrystallization from alcohol raised the melting point to 82–85°. An analytical sample was obtained by precipitation as the hydrochloride salt, filtration, and releasing the amine with dilute NH_4OH: m.p. 83–85°; ν_{max} 1316, 1110 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_9F_2N$: N, 6.45. Found: N, 6.63.

This product was impure and even after acetylation and recrystallization gave low fluorine analyses. The following procedure is far superior.[11]

2.—A mixture of 26.1 g. (0.1 mole) of 5,7-difluoro-2-nitrofluorenone, 87 g. of red P, 100 ml. of 47% HI, and 870 ml. of glacial acetic acid was refluxed for 72 hr. The mixture was boiled down to 300 ml. and diluted with 1.3 l. of water. The hot mixture was filtered, and the filtrate was made alkaline with NH_4OH, giving 21.7 g. (100%) of white product, m.p. 83–85°.

B. Reduction of 5,7-Difluoro-9-oxo-2-fluorenamine.—Reduction of 1.6 g. of the named compound by 47% HI and red P in glacial acetic acid as described for the 4,7-isomer gave the product in 90% yield, m.p. 84–85°.

N-2-(5,7-Difluorofluorenyl)acetamide. A.—Acetylation of the product (m.p. 82–85°), which was obtained in A-1 above,

(9) S. Carpenter, *Dissertation Abstr.*, **19**, 2464 (1959).

(10) For Ullmann syntheses at this batch level we used equipment, fabricated by Mr. D. Hawley, Hawley Engineering, consisting of a 1000-ml. stainless steel, copper-jacketed vessel with thermometer well, equipped with a stirrer having multi-level sets of three blades, a stainless steel air condenser, which is also the stirring shaft, a high-speed motor, and heating tape. The condenser was tightly wound with 6-mm. flattened copper tubing through which a rapid stream of air is blown. We obtain consistently higher yields with this equipment than with conventional round-bottom flask and stirrer. The reaction mixture is extracted with acetone and filtered twice through No. 3 Whatman paper to remove copper and copper halide.

(11) This seems to be the first report of this type of one-step reduction of the nitro group and the keto group together in this series.

from a Wolff–Kishner reaction without catalyst,[12] gave a substance, m.p. 198–203°. After numerous recrystallizations from alcohol, the melting point rose only to 208–210°.[13]

Anal. Calcd. for $C_{15}H_{11}F_2NO$: C, 69.49; H, 4.28; F, 14.66; N, 5.40. Found: C, 70.29; H, 4.74; F, 13.58; N, 5.21.

B.—Acetylation of the product (m.p. 83–85°) described in A-2 above gave a pure product in 80% yield after two recrystallizations from alcohol, m.p. 219.5–220.5°. Admixture with the analytical sample described next showed no depression in melting point; ν_{max} 1290, 1112 (C–F stretching) cm.$^{-1}$.

C.—Acetylation of 4,5-difluoro-2-fluorenamine (prepared by stepwise reduction from the 9-oxo-2-fluorenamine derivative) gave an analytical sample after one recrystallization, m.p. 219.5–220.5°, identical with the preceding substance.

Anal. Calcd. for $C_{15}H_{11}F_2NO$: C, 69.49; H, 4.28; F, 14.66; N, 5.40. Found: C, 69.23; H, 4.21; F, 14.46; N, 5.41.

D.—The foregoing product was also made in small yield by the following three steps.

N-2-(5-Fluoro-7-nitrofluorenyl)acetamide.—Acetylation of 5-fluoro-7-nitro-2-fluorenamine[2a] in benzene gave a product in 87% yield, m.p. 286–289° dec. An analytical sample was prepared by sublimation at 250° (1 mm.), m.p. 288–290° dec., ν_{max} 1269 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{11}FN_2O_3$: N, 9.79. Found: N, 9.80.

N-2-(5-Fluoro-7-aminofluorenyl)acetamide.—Reduction of 5 g. (0.0175 mole) of N-2-(5-fluoro-7-nitrofluorenyl)acetamide in 1.5 l. of boiling alcohol was accomplished with 10 ml. of 85% hydrazine hydrate and 0.1 g. of 5% palladized charcoal.[2c,14] The material went into solution as reduction proceeded. When the reaction was complete the catalyst was filtered off, and the solution was boiled down to give 4.3 g. (96%), m.p. 226–228°. An analytical sample was obtained by recrystallization from alcohol, m.p. 227–228°, ν_{max} 1292 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{13}FN_2O$: C, 70.30; H, 5.11; N, 10.93. Found: C, 70.27; H, 5.35; N, 10.97.

Diazotization of 4 g. (0.0156 mole) of N-2-(5-fluoro-7-aminofluorenyl)acetamide was carried out in the presence of 10 ml. of tetrahydrofuran with 30 ml. of 48% fluoroboric acid and 2 g. of $NaNO_2$ at 0°. The mixture was stirred for 15 min. The salt was filtered off and washed with 1 ml. of methanol, and 1 ml. of ether and dried giving 4.8 g. (87%), dec. pt. *ca.* 205°. It was decomposed in boiling *o*-dichlorobenzene, giving only 0.6 g. of the product, m.p. 189–198°. Recrystallization from alcohol (Darco) gave 0.4 g. (~10%) of material, m.p. 203–205°. This was reacetylated, raising the melting point to 208–210°. The infrared spectrum was identical with those of the pure derivatives in B and C.

N-2-(4-Fluoro-7-acetamidofluorenyl)acetamide.—Acetylation of N-2-(5-fluoro-7-aminofluorenyl)acetamide gave m.p. 330–332 dec. An analytical sample (same melting point) was prepared by recrystallization from alcohol, ν_{max} 1284 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{15}FN_2O_2$: C, 68.44; H, 5.07; F, 6.37. N, 9.73. Found: C, 68.40; H, 5.19; F, 6.00; N, 9.52.

1,3-Difluorofluorenone.[2c]—An Ullmann reaction[10] between 140 g. (0.585 mole) of 3,5-difluoroiodobenzene[2c] and 238 g. (1.1 moles) of methyl *o*-bromobenzoate gave, in addition to 34 g. (27%) of pure product, m.p. 192–192.5° [ν_{max} 1709 (keto C=O), 1311, 1136 (C–F stretching) cm.$^{-1}$] at the usual point in the procedure, 6.7 g. of neutral fraction in the initial separation. This was recrystallized twice from aqueous methanol (Darco) giving 2.1 g., m.p. 190–192°, and proved to be already cyclized product.

Anal. Calcd. for $C_{11}H_6F_2O$: F, 17.58. Found: F, 17.30.

6,8-Difluoro-2-nitrofluorenone.—To 60 ml. of HNO_3 (90%), 32.4 g. (0.15 mole) of 1,3-difluorofluorenone was added in small portions with stirring. The reaction was controlled at 50° or slightly lower. The mixture was allowed to stand at room temperature for 20 min. and poured into 100 ml. of water. The precipitate was filtered off, washed with water and alcohol, and dried giving 36.8 g. (94%), m.p. 246–247°. Crystallization from toluene (Darco) yielded 31.3 g. (80%), m.p. 248–249°. An analytical sample was prepared by sublimation at 220° (1 mm.); m.p. 248.5–249°; ν_{max} 1718 (keto C=O), 1304, 1134 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_5F_2NO_3$: C, 59.78; H, 1.93; N, 5.36. Found: C, 59.98; H, 1.96; N, 5.42.

Single-Step Reduction of 6,8-Difluoro-2-nitrofluorenone.[11]—A mixture of 31.4 g. (0.12 mole) of 6,8-difluoro-2-nitrofluorenone, 70 g. of red P, 85 ml. of 47% HI, and 700 ml. of glacial acetic acid was refluxed for 70 hr. The mixture was boiled down to *ca.* 200 ml., poured into 1.5 l. of hot water, and filtered. The filtrate was made basic with NH_4OH and the precipitate was filtered off, washed with water, and dried, giving 25.1 g. (96%) of 6,8-difluoro-2-fluorenamine, m.p. 164–166°. Recrystallization from benzene (Darco) gave an analytical sample: m.p. 166–166.5°; ν_{max} 1264, 1140 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_9F_2N$: C, 71.83; H, 4.18; N, 6.45. Found: C, 72.19; H, 4.42; N, 6.32.

N-2-(6,8-Difluorofluorenyl)acetamide.—Acetylation of the amine gave an 88% yield, m.p. 212.5–213.5°. An analytical sample, with unchanged melting point, was prepared by recrystallization from alcohol, ν_{max} 1284, 1115 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{11}F_2NO$: C, 69.49; H, 4.23; F, 14.66; N, 5.40. Found: C, 69.64; H, 4.39; F, 14.54; N, 5.50.

6,8-Difluoro-9-oxo-2-fluorenamine.—A mixture of 3 g. (0.0115 mole) of 6,8-difluoro-2-nitrofluorenone, 14 g. of $SnCl_2 \cdot 2H_2O$, 14 ml. of concentrated HCl, and 9 ml. of ethanol was boiled for 20 min. and worked up as usual giving 2.6 g. (97.5%), m.p. 223–224°. Crystallization from toluene raised the melting point to 224–224.5°; ν_{max} 1718 (keto C=O), 1252, 1106 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_7F_2NO$: C, 67.55; H, 3.05; N, 6.06. Found: C, 67.76; H, 3.14; N, 5.89.

N-2-(6,8-Difluoro-9-oxofluorenyl)acetamide.—Acetylation gave the amide: m.p. *ca.* 330° (after recrystallization from alcohol); ν_{max} 1721 (keto C=O), 1318, 1152 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_9F_2NO_2$: N, 5.13. Found: N, 5.05.

1,3,7-Trifluorofluorenone. A. Schiemann Reaction.—To a solution of 1.15 g. (0.005 mole) of 6,8-difluoro-9-oxo-2-fluorenamine in 5 ml. of dimethyl sulfoxide,[8] 15 ml. of 48% fluoroboric acid was added. The mixture was cooled to 0° and diazotized as usual, and the salt (dec. ~175°) was filtered off, washed, and decomposed in boiling *o*-dichlorobenzene, giving 0.7 g. (60%) of crude trifluorofluorenone, m.p. 207–223°. Sublimation at 210° (2 mm.) gave a pure product, m.p. 226–227°. Admixture with the product from the next procedure showed no depression in melting point. The infrared spectra were identical.

B. Ullmann Reaction.—A mixture of 10 g. (0.042 mole) of 3,5-difluoroiodobenzene,[2c] 25 g. (0.106 mole) of methyl 5-fluoro-2-bromobenzoate,[15] and 9 g. of copper was heated at 225° with vigorous stirring for 1.5 hr. An additional 9 g. of copper was added 45 min. from the start and again at the end of 1.5 hr. Heating and stirring were continued for 2 more hr. The mixture was worked up in the usual way to give crude 2,7-difluoro-9-oxofluorene-4-carboxylic acid, m.p. 210–213°, which was crystallized from glacial acetic acid (3 g., m.p. 213–214°). Sublimation at 200° (1 mm.) gave an analytical sample: m.p. 213.5–214.5°; ν_{max} 1740–1695 (strong, broad band, keto C=O and carboxyl C=O), 1277, *ca.* 1235 broad (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_6F_2O_3$: C, 64.62; H, 2.32; F, 14.61. Found: C, 64.43; H, 2.51; F, 14.34.

The residue from the cyclization and alkaline treatment was dried and sublimed at 200° (2 mm.) giving 3.4 g., m.p. 210–225° (sl. residue). Resublimation at 170° (2 mm.) gave 3.2 g. (32.6%) of 1,3,7-trifluorofluorenone: m.p. 226–227°; ν_{max} 1718 (keto C=O), 1277, 1232, 1148 (C–F stretching) cm.$^{-1}$.

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(12) D. Todd, *Org. Reactions*, **4**, 384 (1948).

(13) This modified Wolff–Kishner reaction, successful with some halonitrofluorenones [see (a) K. Suzuki, E. K. Weisburger, and J. H. Weisburger, *J. Org. Chem.*, **26**, 2236 (1961); (b) H. L. Pan and T. L. Fletcher, *J. Med. Chem.*, **7**, 31 (1964)] failed in these reductions, showing loss of fluorine.

(14) Bromo- and chloronitrofluorenes are dehalogenated with Pd–C (but not with Raney Ni) and hydrazine hydrate [T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958)]. The former is advantageous in that the reaction may be started with a suspension of the nitro compound; with Raney nickel nitrofluorenones must first be in solutions or azoxy products result. It is of interest to note that Pd–C induces removal of the $-COCF_3$ from $-NHCOCF_3$ in this type of reduction, whereas Raney nickel leaves the $-COCF_3$ group intact.

(15) First made by H. L. Pan of this laboratory. It came from the 5-nitro ester by reduction (0.5 mole) to 5-amino-2-bromobenzoate. An attempt to distil a moderate amount of this amine at 2 mm. ended in *violent* decomposition. The crude product, $n^{27}D$ 1.6081, was analyzed. *Anal.* Calcd. for $C_8H_8BrNO_2$: C, 41.76; H, 3.51; Br, 34.73; N, 6.09. Found: C, 41.94; H, 3.49; Br, 33.54; N, 6.06. The fluoro compound was made by a Schiemann decomposition of the diazonium fluoroborate giving analytically pure material after distillation.

Anal. Calcd. for $C_{13}H_5F_3O$: C, 66.67; H, 2.15; F, 24.34. Found: C, 66.40; H, 2.39; F, 24.16.

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The Synthesis of DL-*p*-(Hydroxymethyl)phenylalanine

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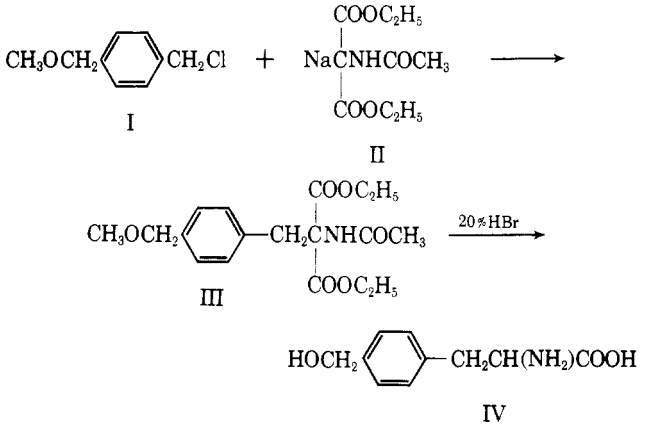
In the course of investigation of the metabolism of certain aromatic amino acids, a study of the properties of *p*-(hydroxymethyl)phenylalanine became of interest. A method for synthesis of this substance was devised (I–IV), patterned after the procedure for preparation of analogous aromatic amino acids used by Herr, *et al.*[2]

Phenylalanine hydroxylase preparations from liver, which form tyrosine from phenylalanine, did not convert *p*-(hydroxymethyl)phenylalanine to tyrosine under the conditions of Udenfriend and Cooper[3] or those of Kaufman.[4] Furthermore, *p*-(hydroxymethyl)phenylalanine in a 4×10^{-3} *M* concentration did not inhibit the oxidation of phenylalanine to tyrosine by the enzyme preparations from rat liver.

Experimental[5]

Diethyl 2-Acetamido-2-[(*p*-methoxymethyl)benzyl]malonate (III).—A solution of 9.8 g. (45 mmoles) of diethyl acetamidomalonate (Calbiochem, Los Angeles, Calif.; recrystallized from toluene; b.p. 96–98°, lit.[6] 96.5–98°) in 35 ml. of absolute ethanol



was added with stirring to a solution of 1.03 g. (44 mg.-atoms) of sodium in 35 ml. of absolute alcohol. *p*-(Methoxymethyl)-benzyl chloride[7] (41 mmoles)[8] was then added, and the mixture was boiled under reflux for 4 hr. The NaCl precipitate was removed by filtration and the filtrate was treated with 100 ml. of water. The oil which formed was separated from the mixture and washed for 1 hr. by suspending it in 650 ml. of water with vigorous stirring to remove residual diethyl acetamidomalonate. The oil was dried by dissolving it in 25 ml. of absolute alcohol and by removing alcohol and water from the solution in a flash evaporator. This treatment was repeated three times. The water-free oil was suspended in 400 ml. of boiling petroleum ether (b.p. 65–110°). The hot solution was filtered to remove a small undissolved residue and was then allowed to stand at room temperature. The white crystals formed were collected by filtration: 9.3 g., m.p. 74–79°. The material was recrystallized from 400 ml. of cyclohexane: yield 8.5 g. (24 mmoles), m.p. 83–85°. Two additional recrystallizations from cyclohexane afforded the analytical sample.

Anal. Calcd. for $C_{15}H_{25}NO_6$: C, 61.5; H, 7.2; N, 4.0; alkoxyl as OCH_3, 26.5. Found: C, 61.5; H, 7.0; N, 3.9; alkoxyl as OCH_3, 26.4.

DL-*p*-(Hydroxymethyl)phenylalanine (IV).—A mixture of diethyl 2-acetamido-2-[(*p*-methoxymethyl)benzyl]malonate (2 g., 5.7 mmoles) and 20% HBr (24 ml.) was heated under reflux for 8 hr. The solution was concentrated to a small volume; the crystalline precipitate formed was collected by filtration and dried at 50° under vacuum: yield 1.6 g., m.p. 198–205° dec.

The crude hydrobromide (1.6 g.) was dissolved in water (200 ml.) and passed through a column (2 × 2 cm.) of the anion-exchange resin Dowex AG 3 X4 (OH⁻ form) to remove HBr. The effluent, approximately pH 6, was concentrated to dryness. The residue was dissolved in 10 ml. of water, treated with 200 mg. of Darco G 60 for 10 min. on a steam bath, and filtered. The residual charcoal was washed with 10 ml. of hot water. The filtrates were combined and evaporated to dryness under reduced pressure. The residue was dissolved in 4 ml. of hot water, 10 ml. of ethanol was added to the heated solution, and the mixture was allowed to stand at 5°. The white precipitate which formed was collected by filtration and dried under vacuum: yield 640 mg. (58%), m.p. 231–237° dec.

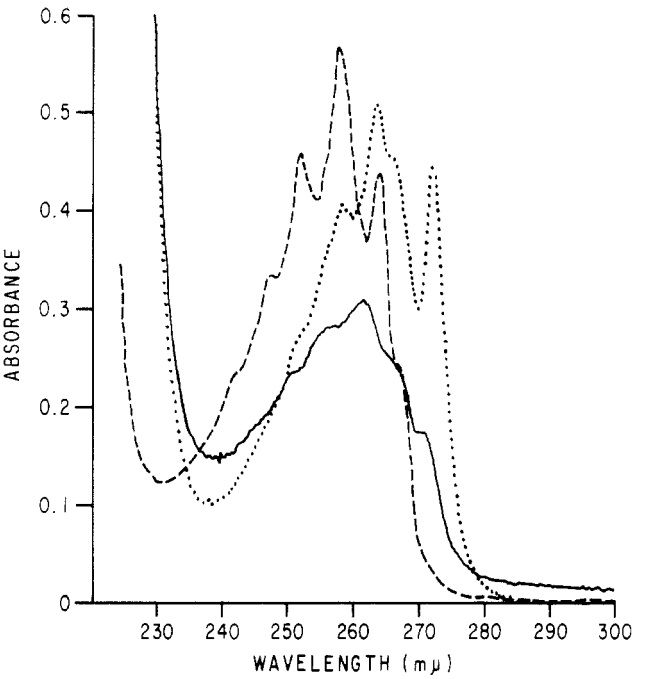


Figure 1.—Ultraviolet spectra of: *p*-(hydroxymethyl)phenylalanine, 0.96×10^{-3} *M*, ———; *p*-methylphenylalanine, 1.4×10^{-3} *M*, ... ; and phenylalanine, 3.0×10^{-3} *M*, – – – . All compounds were dissolved in water.

(1) (a) This investigation was aided by research grants from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service, and a Research Career Award (GM-K6-1551) from the United States Public Health Service. (b) The competent technical assistance of Mr. T. Aogaichi is gratefully acknowledged.

(2) R. R. Herr, T. Enkoji, and J. P. Dailey, *J. Am. Chem. Soc.*, **79**, 4229 (1957).

(3) S. Udenfriend and J. R. Cooper, *J. Biol. Chem.*, **194**, 503 (1952); **196**, 227 (1952).

(4) S. Kaufman, "Methods in Enzymology," Vol. V, S. P. Colowick and N. O. Kaplan, Ed., Academic Press Inc., New York, N. Y., 1962, p. 809.

(5) All melting points are uncorrected. Microanalyses were performed by Australian Microanalytical Service, Parkville, Victoria, Australia. All operations at the boiling points of liquids were done at the prevailing atmospheric pressure (av. 640 mm.).

(6) S. G. Cohen and L. H. Klee, *J. Am. Chem. Soc.*, **82**, 6038 (1960).

(7) R. Quelet, *Bull. soc. chim. France*, **53**, 222 (1933).

(8) The preparation of *p*-(methoxymethyl)benzyl chloride of Quelet[7] also contains the dimethyl ether of *p*-xylene-α,α'-diol in the same fraction (b.p. 120–130° at 15 mm.). The amount of *p*-(methoxymethyl)benzyl chloride in the mixture was determined by estimation of the chlorine content.