TABLE II

OPTICAL DENSITY AT CHARACTERISTIC INFRARED WAVE LENGTHS OF PURE COMPONENTS OF PYROLYSIS MIXTURE IN 0.0288 MM. CELL

Part I Alloöcimene		Part II Dipentene	
Wave Length, Microns	Optical Density	Wave Length, Microns	Optical Density
3.42	1.30	3.43	1.6
6.03	0.300	6.05	0.740
6.91	1.02	6.93	1.23
7.24	0.928	7.25	0.670
7.40	0.460	8.65	0.292
7.85	0.223	8.70	0.285
9.73	0.440	10.94	0.530
10.15	0.838	11.27	1.8
10.50	1.7	12.54	0.685
11.47	0.320	12.67	0.440
11.92	0.300		
12.59	0.770		

Part III α-Pinene		Part IV Ocimene	
Wave Length, Microns	Optical Density	Wave Length, Microns	Optical Density
3.40	2.00	3.40	1.10
6.77	0.635	6.05	0.244
6.88	0.925	6.23	0.372
7.22	0.580	6.91	0.892
7.38	0.790	7.24	0.408
7.50	0.285	9.02	0.645
7.89	0.250	10.12	1.08
8.18	0.290	11.10	1.7
8.87	0.313	11.66	0.310
9.21	0.260	12.10	0.292
9.84	0.350		
10.49	0.250		
11.27	0.384		
12.70	1.32		
12.96	0.287		

TABLE III

OPTICAL DENSITY OF PURE COMPONENTS OF PYROLYSIS MIXTURE IN 0.0288 CELL AT INFRARED WAVE LENGTHS MOST USEFUL IN QUANTITATIVE DETERMINATIONS

Wave Length, Microns	Ocimene	Allo-ocimene	Dipentene	α-Pinene
6.05	0.204	0.240	0.740[a]	0.043
8.65	0.066	0.065	0.292[a]	0.035
8.70	0.044	0.082	0.285[a]	0.032
8.87	0.072	0.057	0.040	0.313[a]
9.02	0.644[a]	0.046	0.076	0.110
9.73	0.118	0.440[a]	0.125	0.118
10.94	0.016	0.450	0.530[a]	0.022
11.64	0.307[a]	0.064	0.060	0.008
12.09	0.319[a]	0.066	0.028	0.013
12.96	0.100	0.067	0.078	0.287[a]

[a] Values, used in calculating composition of mixtures, determined at appropriate wave lengths.

At 9.74 microns, $0.12 (1 - V_2) + 0.44 V_2 = A_s$, where V_2 = vol. fraction of alloöcimene

At 12.96 microns, $0.08 (1 - V_3) + 0.29 V_3 = A_s$, where V_3 = vol. fraction of α-pinene

At 8.70 microns, $0.05 (1 - V_4) + 0.285 V_4 = A_s$, where V_4 = vol. fraction of dipentene

In these equations everything but the component being determined, $(1 - V)$, is treated as one component. A synthetic pyrolysis mixture, Fig. 2, was made with the composition in volume per cent as follows, ocimene 47, dipentene 23, alloöcimene 20, and α-pinene 10. This mixture had an optical density at 12.09 microns of 0.168, at 9.74 microns of 0.183, at 12.96 microns of 0.108, and at 8.70 microns of 0.104. Using the above equations, the following values were obtained: ocimene, 46%; dipentene, 23%; alloöcimene, 20%; and α-pinene, 13%. This is an excellent check with the known values.

GAINESVILLE, FLA.

[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE[1]]

Nitration of 1- and 3-Fluorofluorene

KAZUO SUZUKI,[2] ELIZABETH K. WEISBURGER, AND JOHN H. WEISBURGER

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The nitration of either 1- or 3-fluorofluorene led to a mixture of isomers. In each case, the main product was the 7-nitro derivative, but small amounts of the 2- and 4-nitro compounds were also isolated. The halogen fluorine hinders substitution in the same ring of the polynuclear hydrocarbon fluorene and directs the entering group chiefly into the unsubstituted ring. A number of derivatives of these compounds, including the fluorenones, and the amino and acetylamino derivatives were prepared.

Substitution by the halogen fluorine in molecules with physiological activity has in many cases resulted in a profound alteration of the biological effect tending in general towards an increased activity.[3] With the carcinogen *N*-2-fluorenylacetamide substitution of fluorine at the 7-position served to enhance the carcinogenicity appreciably.[4] The 7-carbon atom is one of the positions at which hydroxylation occurs during the metabolism of

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(3) (a) E. C. Miller and J. A. Miller, *J. Natl. Cancer Inst.*, **15**, 1571 (1955). (b) J. Fried, *Cancer*, **10**, 752 (1957). (c) J. Fried and A. Borman, *Vitamins and Hormones*, **16**, 303 (1958).

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

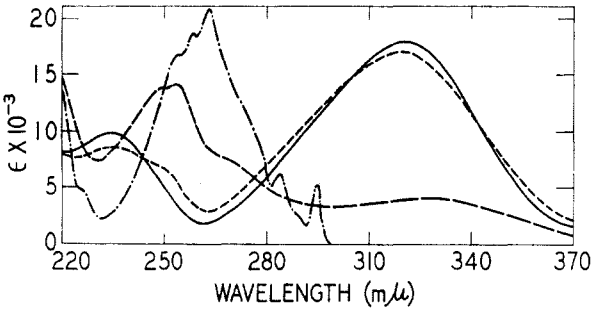


Fig. 1. Ultraviolet absorption spectra: ——— 1-Fluoro-7-nitrofluorene [λ max 234 mμ (ε = 9,800), 320 (17,900); λ min 221 (8,200), 261 (1,800)]: – – – – 1-fluoro-2-n tr - fluorene [λ max 230 (8,470), 237 (8,530), 318 (16,900); λ min 224 (7,670), 234 (8,370), 262 (2,800)]; — — 1-fluoro-4-nitrofluorene [λ max 247 (13,400), 253 (14,000), 336 (4,200); λ min 321 (7,400); 300 (3,400)]; — · — 1-fluorofluorene [λ max 219 (13,800), 227 (4,400), 254 (16,800), 258 (18,600), 263 (20,800), 284 (6,200), 295 (5,100); λ min 232 (2,200), 260 (18,400), 282 (5,100), 292 (1,400). Inflection points are underlined

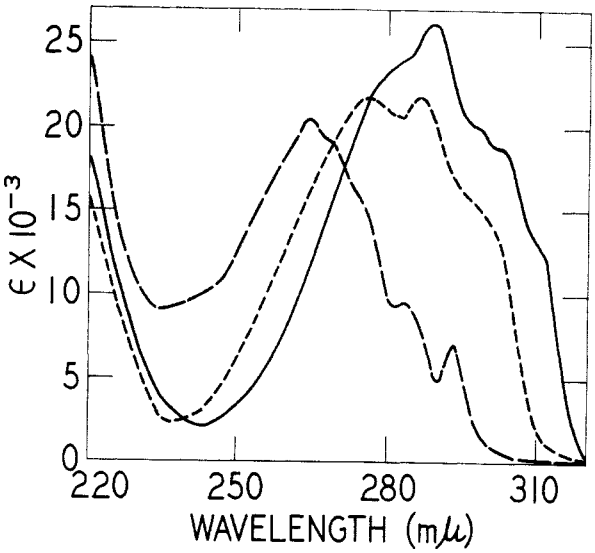


Fig. 2. Ultraviolet absorption spectra: ——— *N*-(8-Fluoro-2-fluorenyl)acetamide [λ max 277 mμ (ε 22,200), 289 (26,200), 297 (20,600), 303 (18,800), 311 (12,600); λ min 243 (2,000), 296 (20,000), 302 (18,600)]; – – – – *N*-(1-fluoro-2-fluorenyl)acetamide [λ max 275 (22,000), 287 (22,000), 302 (14,000); λ min 237 (2,500), 282 (20,800)]; — — *N*-(1-fluoro-4-fluorenyl)acetamide [λ max 264 (20,600), 283 (9,500), 293 (6,000); λ min 235 (9,200), 281 (9,400), 290 (4,800)]

N-2-fluorenylacetamide.[5] Recently the synthesis of *N*-(4- and 5-fluoro-2-fluorenyl)acetamides has been described[6] and the biological testing of these fluoro-substituted derivatives of the carcinogen will be of interest.

Differences in the metabolism of *N*-2-fluorenylacetamide in rats and guinea pigs, species susceptible and nonsusceptible, respectively, to the carcinogenic effect, have focused attention on the *ortho*-hydroxylated derivatives of the carcinogen as possible factors or mediators in the initiation of the carcinogenic process.[7] The question, thus, arose whether carcinogenicity in this series of compounds could be abolished by blocking these *ortho* positions. In this case, also, fluorine was a useful substituent, as carbon-fluorine bonds are stable and the atomic radius of fluorine is not much greater than that of hydrogen.[8] Thus, it was desired to develop syntheses leading to *N*-(1- and 3-fluoro-2-fluorenyl)-acetamides, in which one of the *ortho* positions is occupied by the halogen fluorine.

Initially, it was planned to prepare the intermediates required by nitrating 1- or 3-fluorofluorenes, themselves readily available from the known corresponding amines.[9,10] The experiments, however, indicated that nitration of 1- or 3-fluorofluorene did not occur exclusively at the 2-position but showed instead that a number of isomeric nitro derivatives resulted. The details of the separation and proof of structure of these products form the substance of the present paper.

Compounds derived from 1-fluorofluorene. Nitration of 1-fluorofluorene occurred readily at a temperature of 80° with concentrated nitric acid in acetic acid. The major part of the products crystallized in the reaction mixture in the form of a powder. This material was subjected to a crude fractionation by means of steam distillation. The compounds *A*, m.p. 103°, *A'*, m.p. 112°, *B*, m.p. 133°, and *C*, m.p. 174° were then isolated by a series of systematic fractional crystallizations. The identity of these isomeric 1-fluoro-*x*-nitrofluorenes was ascertained by comparison with an authentic sample, in the case of *B*, and by spectroscopy for the remaining products.

Compound *A'* exhibited an ultraviolet spectrum (Figure 1) remindful of that of 4-nitrofluorene,[11] in contrast to compounds *B* and *C*, whose spectrum was more nearly like that of 2-nitrofluorene. Further evidence for assigning the substituent in compound *A'* to the 4-position was derived from an examination of the spectra of the amine and acetylamino derivative (Experimental and Fig. 2),

(5) J. H. Weisburger, E. K. Weisburger, and H. P. Morris, *Arch. Biochem. Biophys.*, **80**, 187 (1959).

(6) T. L. Fletcher, W. H. Wetzel, M. J. Namkung, and H.-L. Pan, *J. Am. Chem. Soc.*, **81**, 1092 (1959).

(7) (a) J. H. Weisburger, E. K. Weisburger, and H. P. Morris, *Cancer Research*, **18**, 1039 (1958). (b) J. H. Weisburger, E. K. Weisburger, P. H. Grantham, and H. P. Morris, *J. Natl. Cancer Inst.*, **22**, 825 (1959).

(8) (a) L. Pauling, *Nature of the Chemical Bond*, 2nd Ed., Cornell Univ. Press, Ithaca, N. Y., 1940, pp. 160–168. (b) G. W. Wheland, *The Theory of Resonance*, J. Wiley and Sons, Inc., New York, 1944, pp. 97–103.

(9) (a) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **18**, 864 (1953). (b) E. Sawicki and B. Chastain, *J. Org. Chem.*, **21**, 1028 (1956). (c) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **23**, 1193 (1958).

(10) The technical assistance of Mr. Lawrence Shaw in the preparation of 1-fluorenamine is gratefully acknowledged.

(11) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **19**, 964 (1954).

as compared to the curves of similarly 2- and 4-substituted fluorenes.[12] Thus, compound *A'* was 1-fluoro-4-nitrofluorene. Compound *A*, isolated in larger quantities, had an infrared spectrum almost superposable with that of compound *A'*. However, even extensive crystallizations failed to increase the melting point above 103°. Solid solutions and cocrystallizations appear to occur readily in this series of compounds, for similar phenomena were encountered also with the isomeric compound *B*.

Diazotization of 7-nitro-1-fluorenamine[13] in hydrofluoric acid gave a sample of 1-fluoro-7-nitrofluorene, m.p. 145.5°. The infrared spectrum of this compound coincided exactly with that of *B*, m.p. 133°, but the curve of the latter substance exhibited two small additional peaks at 12.87 and 14.30 μ. This quasi-identity of the spectra suggested that these compounds were the same despite the difference in melting points. A phase diagram plotting the melting points versus composition of synthetic mixtures of authentic 1-fluoro-7-nitrofluorene and 1-fluoro-2-nitrofluorene (product *C*) indicates that a material with the melting point of *B* would correspond to a solid solution[14] of about 20% *C* in 80% 1-fluoro-7-nitrofluorene (Figure 3).

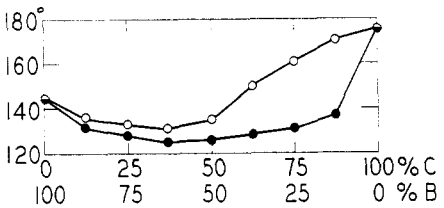


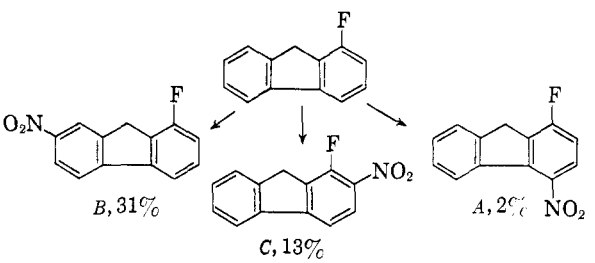
Fig. 3. Phase diagram showing the melting range of mixtures of 1-fluoro-2-nitrofluorene, *C*, and 1-fluoro-7-nitrofluorene, *B*. The mixtures were prepared by taking suitable aliquots of solutions of the pure compounds, followed by removal of the solvent. It seems noteworthy that small amounts of *C* cause but little depression in melting point of *B*, whereas *B* affects the melting point of *C* considerably

The infrared spectrum of such a mixture matched that of *B*. In addition, reduction of *B* gave a crude amine which was resolved by fractional recrystallization into two materials in the ratio of 91 to 9%. The first corresponded to 1-fluoro-7-fluorenamine, the second to 1-fluoro-2-fluorenamine.

Compound *C* also showed an ultraviolet spectrum not unlike that of a 2-substituted fluorene. In view of the fact that the nitro group in *B* was in the 7-position the nitro group in *C* would necessarily be in the symmetrical 2-position. Hence, *C* was 1-fluoro-2-nitrofluorene. A further consideration of the spectra of the amino and acetylamino derivatives likewise confirmed this assignment (*cf.* Experimental Part, Figure 2, and refs. 11,15).

Product *G*, isolated in small amounts from the nitration mixture had an infrared spectrum suggesting the presence of a ketonic function. Oxidation of 1-fluoro-7-nitrofluorene to the fluorenone gave yellow plates, m.p. 212°, identical to compound *G*. Thus, some oxidation to fluorenones occurred during nitration of fluorene derivatives even when the temperature of the reaction was carefully controlled. This observation was made previously in this laboratory with other fluorenes.

These experiments show that 1-fluorofluorene nitrated mainly at the 7-position (31%), and to a lesser extent at the 2- (13%) and 4-positions (2%). The nitration reaction took place at about



the same temperature as that of fluorene itself, and proceeded in a manner similar to that of the unsubstituted hydrocarbon.[16] Nevertheless, the fluorine atom at the 1-position appeared to have some deactivating effect[17] on substitution within the same ring, as the nitration affected chiefly the 7-carbon atom. However, the halogen atom did exhibit some *ortho, para* directivity within the same ring, as demonstrated by the isolation of the 2- and 4-nitro substituted products. Dewar and Urch[15]

(12) J. H. Weisburger, E. K. Weisburger, and H. P. Morris, *J. Am. Chem. Soc.*, **74**, 4540 (1952).

(13) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **21**, 1386 (1956).

(14) It seems that polarizability of the nitro and fluoro radicals in these molecules confers upon them a certain degree of mutual attraction favoring the crystallization of mixtures. The well-known complexing ability of 2,4,7-trinitrofluorenone is based on the presence of 4 such active centers. Reduction of the fluoro-nitro derivatives to the amines removed one of the polarizable groups with a consequent loss of complexing tendencies. Therefore the amines could be readily separated by simple crystallization.

(15) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 3079 (1958).

(16) W. E. Kuhn, *Org. Syntheses*, Coll. Vol. II, 447 (1943).

(17) (a) L. N. Ferguson, *Electron Structures of Organic Molecules*, Prentice-Hall, Inc., New York, N. Y., 1952, p. 296 ff. (b) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 359. (c) In analogy with these findings, it might be expected that fluorine would decrease appreciably the reactivity of the *K* region in the fluoro derivatives of the polycyclic carcinogenic compounds prepared by E. D. Bergmann, J. Blum, S. Butanaro, and A. Heller [*Tetrahedron Letters*, no. 1, 15 1959)]. Since the initiation of the carcinogenic process appears to require reaction at the *K* region [V. T. Oliverio and C. Heidelberger, *Cancer Research*, **18**, 1094 (1958)] it follows that substitution of fluorine at the *K* region would reduce carcinogenicity, rather than increase it, as suggested by Bergmann, *et al.*

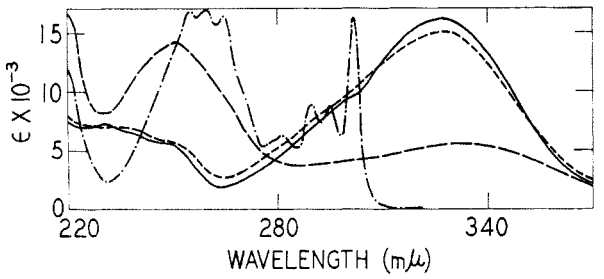


Fig. 4. Ultraviolet absorption spectra: ——— 3-Fluoro-7-nitrofluorene [λ max 230 mμ (ε 7,180), 250 (5,380), 326 (16,100); λ min 224 (6,780), 264 (1,800)]; - - - - 3-fluoro-2-nitrofluorene [λ max 230 (8,270), 245 (5,980), 325 (14,900); λ min 225 (8,170), 264 (2,790)]; — — 3-fluoro-4-nitrofluorene [λ max 220 (16,300), 250 (14,200), 332 (5,600); λ min 230 (8,200), 288 (3,700)]; —·—· 3-fluorofluorene [λ max 221 (11,200), 254 (16,800), 259 (17,000), 265 (16,500), 271 (9,400), 281 (6,300), 290 (9,000), 295 (8,600), 302 (16,200); λ min 231 (2,200), 257 (16,200), 263 (15,400), 275 (5,400), 286 (5,200), 292 (7,600), 298 (6,300)]

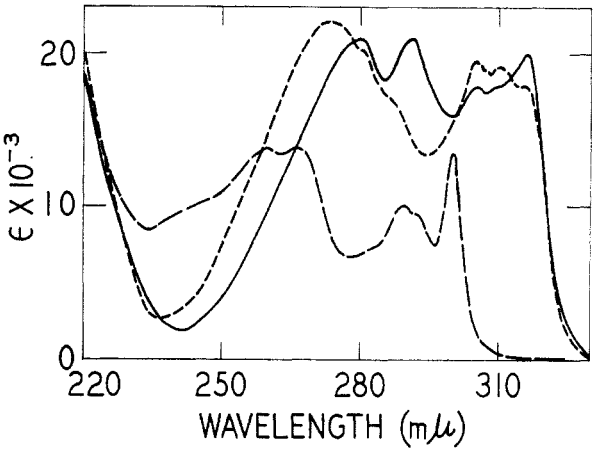


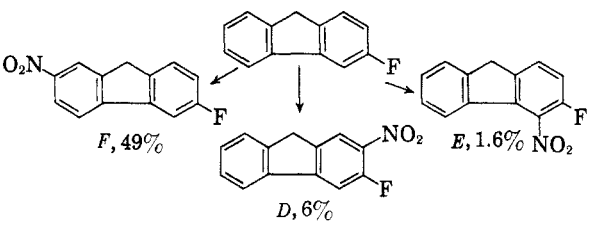
Fig. 5. Ultraviolet absorption spectra: ——— *N*-(6-Fluoro-2-fluorenyl)acetamide [λ max 280 mμ (ε 20,800), 291 (20,800), 304 (17,800), 316 (20,100); λ min 241 (2,000), 285 (18,000), 299 (15,900), 307 (17,600)]; - - - - *N*-(3-fluoro-2-fluorenyl)acetamide [λ max 273 (22,100), 281 (20,300), 305 (19,400), 310 (19,000), 316 (17,900); λ min 237 (2,600), 280 (20,200), 295 (13,400), 308 (18,800), 315 (17,700)]; — — *N*-(3-fluoro-4-fluorenyl)acetamide [λ max 211 (29,800), 259 (13,800), 266 (13,800), 289 (10,000), 300 (13,400); λ min 234 (8,400), 263 (13,400), 278 (6,600), 296 (7,200)]

and we[18] recently reported that fluorene itself upon nitration gave rise to small amounts of 4-nitrofluorene in addition to 2-nitrofluorene.

Compounds derived from 3-fluorofluorene. The nitration of 3-fluorofluorene proceeded under conditions analogous to those used for the 1-isomer. The separation of the isomers produced was somewhat more complex and difficult. However, the combination of fractional crystallizations, steam distillation, and chromatography on alumina yielded four pure compounds: *D*, m.p. 131–132°, *E*, m.p. 146–147°, *F*, 195–196°, and *H*, m.p. 269–271°.

The structure of these compounds was proved, as in the case of the 1-isomer, by comparison with an authentic sample (*F*), and by spectroscopic means for the other materials. The ultraviolet spectrum of 3-fluorofluorene itself, as well as a number of the derived 3-substituted fluorenes (Figs. 4 and 5) have unusual and characteristic features similar to those observed previously with certain other so substituted fluorenes.[9c,19] Compounds *D* and *F* and the amino and acetylamino compounds derived therefrom had spectra which were typically those of a 2-substituted fluorene. In addition, it could be shown by comparison with an authentic sample of 3-fluoro-7-nitrofluorene that the nitro group in compound *F* had entered the 7-position. Thus, it would appear that compound *D* resulted from nitration at the 2-position. Likewise, the spectra of *E*, and compounds derived therefrom were unmistakably those of a 4-substituted fluorene (Figs. 4 and 5), establishing *E* as 3-fluoro-4-nitrofluorene. Oxidation of *D* and *F* produced the corresponding fluorenones. The material *H* was identical to the oxidation product of *F*, 3-fluoro-7-nitrofluorenone.

In essence, the nitration of 3-fluorofluorene produced a complex mixture of isomers. About 49% of the 7-nitro, 6% of the 2-nitro, and 1.6% of the 4-nitro derivatives could be isolated in pure condition.



Catalytic reduction of the nitro derivatives of both 1- and 3-fluorofluorene afforded good yields of the amines,[20] which in turn were acetylated to produce the desired *N*-(fluorofluorenyl)acetamides. However, in view of the preponderance of the materials nitrated at the 7-position, further efforts

(18) E. K. Weisburger and J. H. Weisburger, *Advances in Cancer Research*, V, 331 (1958).

(19) N. Ishikawa and M. Okazaki, *Yûki Gôsei Kagaku Kyôkai Shi*, 16, 610 (1958).

(20) The ionization constants of the amines[21] in 70% ethanol offer further proof that the structures assigned to the nitro compounds are correct. Fluorine in an *ortho* position to the amino group has a larger depressing effect on the *p*K than in other positions. Values, determined at 25°, were as follows: 1-fluoro-2-fluorenamine, 2.59; 1-fluoro-4-fluorenamine, 2.95; 8-fluoro-2-fluorenamine, 3.54; 3-fluoro-2-fluorenamine, 2.69; 3-fluoro-4-fluorenamine, 2.71; 6-fluoro-2-fluorenamine, 3.71; 7-fluoro-2-fluorenamine[4] 3.53; 5-fluoro-2-fluorenamine,[6] 3.93; 4-fluoro-2-fluorenamine[6] 3.05 (we are grateful to Drs. J. and E. Miller, University of Wisconsin, for providing the last 3 compounds). For reference, 2- and 4-fluorenamine had *p*K values of 4.27 and 3.15, respectively.

(21) P. H. Grantham, E. K. Weisburger, and J. H. Weisburger, 125th Meeting, American Association Advancement Science, Washington, D. C., December 1958, General Program, p. 168. Manuscript in preparation.

are required to develop more specific methods of synthesis for the preparation of the larger amounts of the *ortho*-substituted *N*-(1- and 3-fluoro-2-fluorenyl)acetamides necessary for biological experiments.

EXPERIMENTAL

The melting points were determined in a capillary tube and are uncorrected. The ultraviolet absorption spectra were recorded by Mr. P. H. Grantham on a Cary recording spectrophotometer as 5×10^{-5} molar solutions in ethanol and the infrared spectra on a Perkin Elmer spectrophotometer, model 21, as solids in potassium bromide disks. We are indebted to Dr. W. C. Alford, and Mr. R. Koegel, and their staffs, for the microanalyses.

Derivatives of 1-fluorofluorene. 1-Fluorofluorene.[22] Powdered 1-aminofluorene[9a,b] (7.5 g.) was stirred with 375 ml. of 52% technical hydrofluoric acid in a polyethylene beaker, yielding initially a solution from which a salt precipitated on cooling to 5°. Over a period of 30 minutes 2.92 g. of powdered sodium nitrite was added with stirring. The mixture was allowed to stand in the cold for 3–4 hr. and then at 25° 24–48 hr. longer. The precipitated material (8.6 g.) was filtered off and washed with water. Extraction with 0.5*N* potassium hydroxide, followed by acidification of the extract afforded 106 mg. of 1-fluorenol, m.p. and mixed m.p. 117–118°.[9a] The main residue was extracted with 250 ml. of refluxing petroleum ether. The solution was taken to dryness and the residue was sublimed at 1 mm. pressure and a bath temperature of 60°, yielding 6.17 g. (81%) of 1-fluorofluorene, m.p. 81–83°. Recrystallization from dilute ethanol or dilute acetic acid raised the melting point to 83–84°; carbon-fluorine stretching: 8.09 μ.

Anal. Calcd. for $C_{13}H_9F$: C, 84.76; H, 4.92. Found: C, 84.54; H, 5.19.

1-Fluoro-7-nitrofluorene. By a similar procedure, 226 mg. of 7-nitro-1-fluorenamine[13] in 80 ml. of hydrofluoric acid was diazotized with 80 mg. of sodium nitrite yielding 220 mg. of product. Sublimation at 1 mm. pressure for 5 hr. at a bath temperature of 90–100° afforded 160 mg. of almost colorless material, m.p. 144–145°, which when chromatographed on alumina (Merck, suitable for chromatographic adsorption) in benzene solution and recrystallized from cyclohexane gave 126 mg. of 1-fluoro-7-nitrofluorene, m.p. 144–145°. The analytical sample, which was crystallized from ethanol and 50% aqueous acetic acid, melted at 145–145.5°.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.85; H, 3.61.

Nitration of 1-fluorofluorene. The reaction used for fluorene[16] was modified by altering the proportion of nitric to acetic acid. Seventeen ml. of concentrated nitric acid (d = 1.42) was added to a solution of 10 g. of 1-fluorofluorene in 30 ml. of acetic acid at 50°. By means of a water bath the temperature was raised to 80° and maintained thereat for 15 minutes. An exothermic reaction was accompanied by the crystallization of products. After cooling to 25° and standing overnight, the solids weighing 9.9 g., m.p. 120–133°, were filtered off. The filtrate from the reaction mixture was treated as described later.

Steam distillation gave a volatile fraction, 1.92 g., m.p. 79–93°, which by fractional crystallization from petroleum ether gave 535 mg. of compound *B*, m.p. 133°, 5 mg. of A′, *1-fluoro-4-nitrofluorene*, m.p. 111–112°, and 128 mg. of compound *A*, (a mixture of the 4- and 2-nitro isomers), m.p. 100–103°. The analytical sample melted at 103°, and, being a solid solution with an isomer, analyzed correctly.

(22) The procedure was patterned after that developed by W. M. Stanley, E. McMahon, and R. Adams, *J. Am. Chem. Soc.*, **55**, 706 (1933).

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.91; H, 3.69.

The residue from the steam distillation, 7.5 g., m.p. 130–143°, was extracted twice with 300 ml. of ethanol. The extracts were taken to dryness. The residue was recrystallized from ethanol, yielding 3.25 g. of product *B*, m.p. 130–132°. From the mother liquors 0.2 g. of material, m.p. 157–165° was isolated. This, combined with the insoluble portion, 2.24 g., m.p. 162–165°, from the ethanol extractions, was recrystallized from acetic acid affording 1.62 g. of product *C*, m.p. 173–174°.

The following operations were performed in the hope of purifying 1.08 g. of product *B*. Crystallization from cyclohexane (842 mg., m.p. 132–133°), crystallization from ethanol (420 mg., m.p. 133–134°), sublimation at 1 mm., 90° bath (403 mg. sublimate, m.p. 133–134.5°, and 17 mg. residue, m.p. 133°), recrystallizations of the sublimate from ethanol and cyclohexane (200 mg., m.p. 133.5–134°). Apparently, *1-fluoro-7-nitrofluorene* formed an unresolvable solid solution with the isomeric 1-fluoro-2-nitrofluorene.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.92; H, 3.61.

Product *C*, *1-fluoro-2-nitrofluorene*, was recrystallized twice from acetic acid, m.p. 177–178°.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.89; H, 3.68.

Oxidation of this compound gave *1-fluoro-2-nitrofluorenone*, m.p. 231–232°, after recrystallization from acetic acid. Ultraviolet spectrum: λ_{max} 242 mμ (ϵ = 21,300), 282 (22,100), 375–380 (2,500); λ_{min} 262 (15,100), 350 (2,050).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49. Found: C, 64.13; H, 2.79.

The filtrate from the reaction mixture was diluted with water yielding an oil which was taken up in benzene. The extract was washed with 1*N* potassium hydroxide solution and water, then dried over calcium chloride and chromatographed on alumina. The first fraction, a light yellow solution, upon evaporation and crystallization of the residue from ethanol and petroleum ether, afforded 126 mg. of compound *A*. Three further fractions gave brown to reddish oils which were discarded.

The fifth fraction, upon removal of the solvent, left a yellow solid which was crystallized from ethanol to yield 10 mg. of compound *G*, m.p. 211–212°, exhibiting a strong carbonyl absorption at 5.85 μ, and C–F stretching at 8.10 μ. Melting and mixed melting points and infrared spectra proved the identity of this material with authentic 1-fluoro-7-nitrofluorenone.

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49. Found: C, 63.97; H, 2.73.

1-Fluoro-7-nitrofluorenone. A mixture of 42 mg. of 1-fluoro-7-nitrofluorene, m.p. 145°, 85 mg. of chromium trioxide, and 5 ml. of acetic acid was refluxed for 3 hr. and poured into cold acidulated water. Upon recrystallization from acetic acid 14 mg. of small yellow plates of the fluorenone, m.p. 211–212° was obtained. Ultraviolet spectrum: λ_{max} 237 mμ (ϵ = 22,800), 282 (22,500), 305 (13,900), 370–375 (2,700); λ_{min} 260 (14,700), 301 (13,300), 353 (2,300).

1-Fluoro-2-fluorenamine. Low pressure catalytic reduction (Parr shaker) over platinum oxide of 2 g. of 1-fluoro-2-nitrofluorene in 80 ml. of ethanol followed by partial evaporation of the solvent (nitrogen atmosphere) and addition of water gave 1.74 g. of the amine, m.p. 109–110°. Recrystallization from water, cyclohexane, and 50% ethanol raised the melting point to 115–116°; λ_{max} 290 mμ (ϵ = 21,900); λ_{min} 244 mμ (ϵ = 1,590); C-F stretching; 8.23 μ.

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.06. Found: C, 78.37; H, 5.34.

N-(1-Fluoro-2-fluorenyl)acetamide. Brief refluxing of 1 g. of the amine in 30 ml. of benzene and 1.2 ml. of acetic anhydride gave 1.02 g. of the acetyl derivative, m.p. 178–179°. Crystallization from ethanol afforded 820 mg. of colorless needles, m.p. 179.5–181°. After further crystallizations

from benzene and ethanol the melting point remained unchanged at 180.5–181.5°.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.02. Found: C, 74.41; H, 5.19.

1-Fluoro-4-fluorenamine. Catalytic reduction of 220 mg. of 1-fluoro-4-nitrofluorene, m.p. 103°, gave 147 mg. of amine, m.p. 78°. Crystallization from water, and cyclohexane increased the melting point to 79–80°; λ_{max} (main peaks only given of the characteristically complex curve) 216.5 mμ (ϵ = 29,700), 261.5 (15,100), 266 (14,500), 271 (17,900), 320 (6,280); λ_{min} 214 (29,400), 252.5 (10,400), 287 (3,390). Carbon-fluorine stretching: 8.12 μ.

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.06. Found: C, 77.82; H, 4.91.

N-(1-Fluoro-4-fluorenyl)acetamide. A solution of 100 mg. of the amine in 3 ml. of benzene and 0.12 ml. of acetic anhydride was warmed on the steam bath for 25 minutes to give, on cooling, 94 mg. of white crystals, m.p. 218–223°. Crystallizations from benzene, and ethanol left 60 mg. of compound, m.p. 228–230°; C—F stretching: 8.12 μ.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.02. Found: C, 74.79; H, 5.63.

1-Fluoro-7-fluorenamine. A. Reduction of 241 mg. of 1-fluoro-7-nitrofluorene, m.p. 143°, afforded 168 mg. of colorless long needles m.p. 143–144°, after one crystallization from cyclohexane.

B. Reduction of 2 g. of compound *B*, m.p. 133°, gave 1.66 g. of product with a melting range of 122–127°. Recrystallization from cyclohexane produced 1.05 g. of crystals, m.p. 137–139°. By evaporation of the mother liquor 109 mg. of material, m.p. 109–110° was obtained. Separate recrystallization of these samples from cyclohexane yielded 53 mg. of 1-fluoro-2-fluorenamine, m.p. 114–115°, identical to the previously described compound, and 888 mg. of 1-fluoro-7-fluorenamine, m.p. 141–143°, equal in all respects to the material obtained under *A* above. λ_{max} 293 mμ (ϵ = 20,900); λ_{min} 246.5 mμ (ϵ = 1,890). C—F stretching: 8.17 mμ.

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.06. Found: C, 78.16; H, 5.31.

N-(8-Fluoro-2-fluorenyl)acetamide. Acetylation of 500 mg. of amine in 15 ml. of benzene with 0.6 ml. of acetic anhydride gave 556 mg. of the acetyl derivative, m.p. 186–187°. C—F stretching: 8.11 μ.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.02. Found: C, 74.49; H, 5.01.

Derivatives of 3-fluorofluorene. 3-Fluorofluorene. A. An ice-cold solution of 1.9 g. of 3-fluorenamine[9c] in 50 ml. of 52% hydrofluoric acid was treated with 750 mg. of sodium nitrite. After standing at 25° for 2 days, 1.57 g. of brown material was filtered off and washed with water. Sublimation at 1 mm. pressure at a bath temperature of 90–100° yielded 1.02 g. of sublimate which was chromatographed on alumina in benzene solution. Removal of the solvent afforded 863 mg. of slightly yellowish product, m.p. 77–78°, which upon resublimation gave 789 mg. of 3-fluorofluorene as a white powder with the same melting point. Elution of the alumina column, above, with ethanol, followed by crystallization yielded, in addition, 89 mg. of 3-fluorenol, m.p. and mixed m.p. 137–138°.[9c]

B. A hot solution of 30 g. of 3-fluorenamine in 260 ml. of 1*N* hydrochloric acid was filtered and 300 ml. of 12*N* acid was added. The ice-cold mixture was diazotized by introducing 11.8 g. of sodium nitrite in 66 ml. of water all at once. After stirring for 0.5 hr., 158 ml. of a sodium fluoborate solution[23] caused the precipitation of the fluoborate (42.6 g., m.p. 123° with decomposition), which was filtered off after standing overnight at 2°. This material was decomposed by heating cautiously with a direct flame. The product was extracted with hot petroleum ether. After evaporation of the solvent and sublimation of the residue *in vacuo*, recrystallization from 50% ethanol yielded 15 g. of 3-fluorofluorene, m.p. 76°. Further crystallization from dilute ethanol, and acetic acid raised the melting point to 77–78°. C—F stretching: 8.52 μ.

Anal. Calcd. for $C_{13}H_9F$: C, 84.76; H, 4.92. Found: C, 84.91; H, 5.23.

3-Fluoro-7-nitrofluorene. A mixture of 1 g. of 7-nitro-3-fluorenamine,[9c] 90 ml. of 52% hydrofluoric acid, and 335 mg. of sodium nitrite was allowed to stand for 2 days, then was briefly warmed on a steambath. The precipitate was filtered off (342 mg., m.p. 183–189°), and sublimed *in vacuo* at a bath temperature of 170°. A solution of the sublimate in benzene was percolated through an alumina column. The solvent was removed and the residue crystallized from acetic acid yielding 128 mg. of pale yellow needles, m.p. 198°. Further crystallizations from benzene and acetic acid gave a pure sample, m.p. 199–200°. C—F stretching: 8.52 μ.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 68.09; H, 3.75.

Nitration of 3-fluorofluorene. The nitration was performed as described for the 1-isomer, yielding 11.1 g. of solid, m.p. 155–174°, and the mother liquor which was worked up separately. The solid was refluxed with 550 ml. of ethanol (some material remained undissolved) and cooled. The resulting insoluble material was recrystallized from acetic acid to yield 5.4 g. of compound *F*, m.p. 196°. By mixed melting point and identical infrared spectra *F* was shown to be *3-fluoro-7-nitrofluorene.*

The ethanolic mother liquor was steam-distilled. The residue (3.4 g., m.p. 132–140°) was chromatographed on alumina in benzene solution, giving two main fractions weighing 1.3 g., m.p. 147–166°, and 1.1 g., m.p. 125–133°. Fractional crystallizations of each from benzene and ethanol afforded 448 mg. of compound *D*, m.p. 132°, 116 mg. of compound *F*, m.p. 196°, and 562 mg. of an impure fraction *F'*, which when combined with similar fractions obtained in other parts of the isolation steps finally gave 510 mg. of *F*.

The material volatile in steam (1.1 g., m.p. 94–110°) was chromatographed on alumina in cyclohexane-benzene (1:2). Upon recrystallization of the fractions so derived, 177 mg. of *D*, 195 mg. of *E*, m.p. 146°, and 50 mg. of *F'*, could be isolated.

The filtrate from the reaction mother liquor was diluted with water and partially neutralized with sodium acetate. The resulting oil was taken up in benzene. After washing the solution with 1*N* alkali and water and drying, the solution was chromatographed on alumina. Recrystallization of the various fractions obtained by taking the eluates to dryness gave 137 mg. of compound *D*, 18 mg. of compound *E*, 10 mg. of *F'*, and 2.5 mg. of compound *H*, m.p. 271°. The last named material was identical with 3-fluoro-7-nitrofluorenone as proved by mixed melting point and superposable infrared spectra.

Recrystallization of compound *D* from ethanol, dilute acetic acid, and cyclohexane gave small white needles of *3-fluoro-2-nitrofluorene,* m.p. 134.5–135.5°; C—F stretching: 8.40 μ.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 68.01; H, 3.54.

Oxidation of this compound gave *3-fluoro-2-nitrofluorenone,*[24] m.p. 220–221°, after recrystallization from acetic acid. λ_{max} 242 mμ (ϵ = 22,700), 257 (20,100), 277 (22,200), 300 (12,600), 323 (5,960), 338 (5,200); λ_{min} 253 (19,800), 264 (19,100), 317 (5,600), 333 (4,900).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49. Found: C, 63.69; H, 2.66.

Similar purification of compound *E* afforded pale yellow,

(23) A. Roe, *Org. Reactions,* V, 193 (1949).

(24) This compound may be identical to a 3-(or 1-)-fluoro-2-nitrofluorenone, m.p. 224–224.5°, described by W. H. Wetzel, M. J. Namkung, H.-L. Pan, and T. L. Fletcher, 134th National Meeting, American Chemical Society, Chicago, Ill., September, 1958, Abstracts of papers, p. 25-0.

long needles of *3-fluoro-4-nitrofluorene*, m.p. 147–147.5°; C—F stretching: 8.44 μ.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.63; H, 3.46.

3-Fluoro-7-nitrofluorenone. Oxidation of 100 mg. of the fluorene derivative by 200 mg. of chromium trioxide in 5 ml. of acetic acid yielded 48 mg. of yellow needles, m.p. 276–277°, after crystallization from acetic acid. Main peaks in ultraviolet spectrum: λ_{max} 241.5 mμ (ϵ = 18,100), 282 (23,100), 323 (4320), 337.5 (3440); λ_{min} 258 (12,600), 317 (3,940), 332 (3250).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49. Found: C, 64.34; H, 2.78.

3-Fluorofluorenamines and acetyl derivatives. The isomeric 3-fluoronitrofluorenes were reduced catalytically (platinum oxide) in ethanol solution in 80–90% yields. The acetyl derivatives were produced in similar yields by the action of acetic anhydride on a benzene solution of the amines. Pertinent data for the compounds are listed below. *3-Fluoro-2-fluorenamine*, m.p. 131–131.5° (from water, cyclohexane). λ_{max} 282 mμ (ϵ = 18,700), 320 (12,600); λ_{min} 243.5 (1,790), 308.5 (11,400). C—F band, 8.66 μ.

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.06. Found: C, 78.94; H, 5.26.

N-(3-Fluoro-2-fluorenyl)acetamide, m.p. 194–195° (from ethanol). C—F band, 8.64 μ.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.02. Found: C, 74.24; H, 4.96.

3-Fluoro-4-fluorenamine, m.p. 118–119° (from water, cyclohexane). Ultraviolet spectrum (main peaks of complex curve): λ_{max} 213 mμ (ϵ = 26,100), 250 (11,400), 261 (11,800), 270 (13,100), 299 (6,400), 315 (6,100); λ_{min} 242 (10,000), 279 (4,300). C—F band, 8.48–8.55 μ.

Anal. Found: C, 78.26; H, 5.31.

N-(3-Fluoro-4-fluorenyl)acetamide, m.p. 227–228° (from benzene). C—F band, 8.55 μ.

Anal. Found: C, 74.57; H, 5.20.

6-Fluoro-2-fluorenamine, m.p. 125–126° (from aqueous ethanol, water, cyclohexane) obtained by reduction of 3-fluoro-7-nitrofluorene. λ_{max} 295 mμ (ϵ = 17,900); λ_{min} 245 (2,090). C—F band, 8.58 μ.

Anal. Found: C, 78.29; H, 5.06.

N-(6-Fluoro-2-fluorenyl)acetamide, m.p. 198–199° (from ethanol). C—F band, 8.52 μ.

Anal. Found: C, 74.71; H, 5.24.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Adrenal Hormones and Related Compounds. V.[1] 2-Fluorinated Cortical Hormones

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A preparation of 2-fluoro-Δ^4-3-ketosteroids is described, making use of the reaction of perchloryl fluoride with the enolates of 2-ethoxyoxalyl-Δ^4-3-ketosteroids. By applying this procedure to the cortical hormone precursors 11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one (Ia) and the corresponding 6α-methyl derivative (Ib), the 2-fluoro derivatives of hydrocortisone acetate (IIIa) and 6α-methylhydrocortisone acetate (IIIb) have been prepared.

Marked modification of hormonal properties of steroids is brought about by substitution of fluorine at the 6[2a], 9[2b], or 12[2c] positions. We have now prepared some cortical hormone derivatives with fluorine substituted at C-2.[3]

The activation of a ring or side chain α-ketone position of a steroid by ethoxalylation to facilitate and direct electrophilic substitution by alkyl halide[4] or halogen,[5] respectively, has been described. Perchloryl fluoride, which has recently been found capable of fluorinating carbanions under mild conditions,[6] has now been employed with steroid 2-ethoxalylates, and has been found to produce simply and in good yields the correspondingly substituted fluoro steroids.

Direct ethoxalylation of the cortical hormones was previously found unsatisfactory[7] as a route to the 2 - methyl derivatives. The preferred intermediate was 11β-hydroxy-21-acetoxy-4,17(20)-[*cis*]-pregnadien-3-one (Ia, R′ = Ac),[4] which was

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(7) Unpublished results obtained in connection with the work reported in ref. (4).