[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

Sulfur Derivatives of Fluorene[1]

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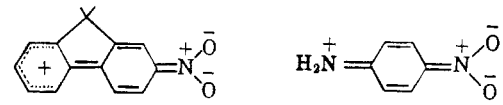
2-Mesyloxy-, 2-mesylamino-, 2-methylmesylamino-, and 2-mesylfluorene; 2-mesylfluorenone, 2-mesyl-7-aminofluorene, and 2-mesyl-7-acetylaminofluorene, as well as ten 2-alkylthio- and 2-N-alkylsulfonamido-fluorene derivatives have been prepared. Nitration of 2-mesylfluorene gave 2-mesyl-7 nitro- and 2-mesyl-5-nitro-fluorene. The structures of these derivatives were proven by a comparison of the ultraviolet absorption spectra of related fluorene compounds. The absorption spectra of 26 fluorene derivatives are discussed in reference to chemical carcinogenesis.

Many aromatic amines and their derivatives are known to have cancer-producing activity in mammals.[2] Substitution of a hydrogen, a hydroxyl, a halogen or alkyl group for the amino group has been reported to cause a loss of activity.[2] If the carcinogenic activity of these aromatic amines is in any way related to the manner of interaction of the unshared pair of electrons on the amino nitrogen with the unsaturation electrons of the parent hydrocarbon, then groups with a similar type of electronic distribution should be able to replace the amino group with not too large a loss in activity. As far as this electronic distribution similarity is concerned, the ultraviolet spectra show that the thio groups are more closely similar to the analogous amino groups than are the other miscellaneous groups, Table I, although the amino group is undoubtedly the much more powerful auxochrome. On the basis that the thio group resembles the amino group electronically, appropriately substituted aromatic thio derivatives should be checked for carcinogenic activity.

As not many fluorene sulfur derivatives are known, various types have been synthesized for the dual purpose of eventual testing of carcinogenic activity and spectroscopic comparison with other kinds of fluorene derivatives. A comparison of the ultraviolet spectra of 2-substituted fluorene derivatives in Table I indicates that the nitro group is, as to be expected, the most powerful electronegative substituent. The spectra of 2-nitrofluorene and, to a lesser extent, of 2-acetylfluorene show the typical *p*-nitroaniline type of envelope. This consists of a narrow band of fairly strong intensity in the ultraviolet and a much more intense broad band at or near the visible end of the spectrum. The similarity in spectral envelopes of 2-nitrofluorene and *p*-nitroaniline type molecules is probably due to the similarity of the principal excited states, *e.g.*



Many phenols and anilines substituted in the *para* position with an electron-attracting group have this type of spectral envelope.[3] 2-Fluorenols and 2-fluorenamines with an electronegative group in the extended *para* position also show this type of spectrum.[4]

On the other hand the simple mesyl (CH_3SO_2—) and sulfonamido derivatives have typical fluorene-type spectra. This is an indication of the weak electronegative character of these groups. The bathochromic effect of the alkyl, chloro, hydroxy, and amino groups increased in that order. The acetylthio and alkylthio groups had a bathochromic effect which was second only to that of the analogous amino substituents. Acyl substitution for the alkyl groups in the alkoxy, alkylthio, and dialkylamino compounds caused a hypsochromic shift. The spectra of all these compounds were very similar to the spectrum of fluorene except for the gradual disappearance of the fine structure as the substituents became more powerful electron donors.

The alkylthio derivatives of fluorene were obtained by the reaction of 2-acetylthiofluorene with alkyl halides in alkaline solution. The oxidation of 2-methylthiofluorene gave 2-mesylfluorene. The structure of the latter compound was shown by the analytical data and the presence in the infrared spectrum of bands in chloroform at 7.61 and 8.79 μ which are evidently the asymmetrical and symmetrical stretching frequencies of the sulfone group. The reported asymmetrical and symmetrical stretching frequencies for sulfones are 7.5–8.0 μ and approximately 9 μ, respectively.[5]

The nitration of 2-mesylfluorene gave two mononitrated products, one melting at 299–300° with decomposition and the other at 197–199°. The spectra of these two compounds are shown in Fig. 1. The absorption spectra of the higher melting compound, λ_{max} 249, 317 mμ and log ϵ 4.00, 4.37, re-

(1) This investigation was supported by research grants C-1308 and C-1066 from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

(2) Hartwell, *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*, 2nd Ed., Superintendent of Documents, Washington, D.C., 1951.

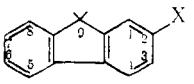
(3) Kumler, *J. Am. Chem. Soc.*, **68**, 1184 (1946).

(4) Sawicki and Wade, *J. Org. Chem.*, **19**, 1109 (1954).

(5) Barnard, Fabian, and Koch, *J. Chem. Soc.*, 2442 (1949).

TABLE I

ULTRAVIOLET SPECTRAL DATA OF 2-SUBSTITUTED FLUORENE DERIVATIVES



X	Main Bands λ max, mμ	Log ε	Subsidiary Bands λ max, mμ	Log ε
Nitro	232–234	3.98		
	330–333	4.26		
Acetyl	218[a]	4.21		
	295–296	4.32		
	313	4.42		
N,N-Di-*n*-butylsulfonamide	280	4.39	293	4.29
			304	4.34
Mesyl	277–278	4.35	292	4.24
			302	4.27
H	260	4.28	289	3.78
			294	3.68
			300	3.94
Mesyloxy	264	4.34	291	3.84
			302	3.93
Acetoxy	264	4.34	292	3.82
			295	3.79
			303	3.90
Methyl	265	4.32	293	3.80
	275	4.16	298	3.75
			305	3.90
Ethyl	266	4.34	293	3.84
	275	4.20	297	3.78
			304	3.95
Chloro	266	4.36	295	3.82
			298	3.81
			306	3.86
p-Nitrobenzenesulfonylamino	270	4.39	300	3.99
			330[b]	3.35
Methylmesylamino	269–270	4.36	292	3.98
			302	3.98
Methoxy	271	4.34	303	3.81
			314	3.79
Hydroxy	272	4.29	305–307	3.76
			309	3.75
			314	3.75
Mesylamino	274	4.37	304	3.91
N-Methyl-N-*p*-tosylamino	273–274	4.36	293	4.13
			303	4.10
p-Tosylamino	275	4.36	302–303	4.04
Mesylthio	276–278	4.49	308	4.35
Acetylthio	276–278	4.37	291	4.24
			304	4.24
Amino	287–288	4.32	315	3.94
Acetylamino	281–282	4.40	301	4.25
	288	4.43	313–314	4.13
Methylthio	290	4.38	approx. 315	4.05
Ethylthio	291	4.35	301	4.25
Cyclopentylthio	293	4.34	304	4.26
Dimethylamino	303	4.36	325	4.10
Diethylamino	308	4.42	approx. 340	4.02

[a] Underlined values are shoulders or inflection points. [b] This strong shoulder is mainly due to the nitrobenzene part of the molecule.

spectively, and 2,7-dinitrofluorene, λ_{max} 240, 331 mμ and log ε 3.9, 4.5, respectively, are fairly similar. They both have the *p*-nitroaniline type of spectrum.

Further evidence that the higher melting compound is 2-mesyl-7-nitrofluorene is provided by the spectrum of the derived amine, Fig. 1, which has

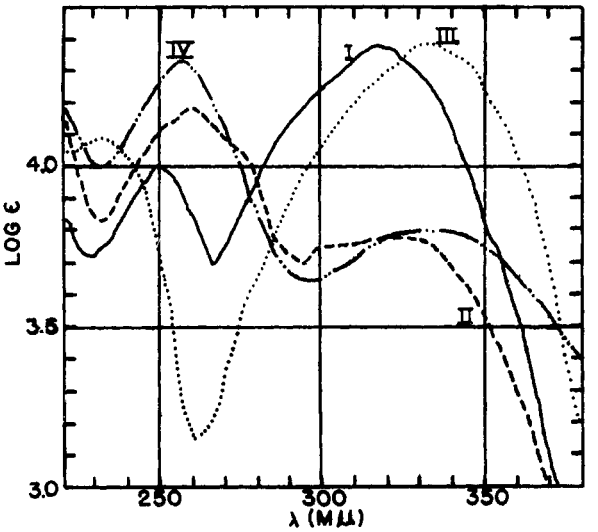


FIG. 1.—ULTRAVIOLET ABSORPTION SPECTRA: I, 2-Mesyl-7-nitrofluorene (————); II, 2-mesyl-5-nitrofluorene (– – –); III, 2-mesyl-7-aminofluorene (· · ·); IV, 4-nitrofluorene[7] (— · · — · ·).

the typical *p*-nitroaniline type of spectrum characteristic of benzene and biphenyl compounds containing an electron-donating and an electron-attracting group in the *para* positions. As to be expected, 2-mesyl-7-aminofluorene, λ_{max} 230, 332 mμ and log ε 4.09 and 4.38, respectively, and 2-acetyl-7-hydroxyfluorene,[4] λ_{max} 233, 331 mμ and log ε 4.12 and 4.45, respectively, have similar spectra.

As the nitration of 2-nitrofluorene gives mainly the symmetrical 2,7-dinitrofluorene, m.p. 295–300° dec, and the more soluble 2,5-dinitrofluorene, m.p. 207°[6] it is probable that the nitro-2-mesylfluorene, m.p. 197–199°, is the 2,5-derivative. This is confirmed by the similarity of the spectrum of the latter compound and 4-nitrofluorene,[7] Fig. 1.

In previous papers 7-methyl, 7-ethyl,[8] and 7-acetyl[4] derivatives of the carcinogenic[9] 2-acetylaminofluorene were reported. For a further comparison of physical and carcinogenic properties 2-mesyl-7-acetylaminofluorene was synthesized.

EXPERIMENTAL[10]

General procedure for the preparation of alkylthiofluorenes. To a solution of 2.4 g. (0.01 mole) of 2-acetylthiofluorene[11]

(6) Morgan and Thomason, *J. Chem. Soc.*, 2691 (1926).

(7) Weisburger and Weisburger, *J. Org. Chem.*, **19**, 964 (1954).

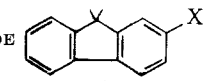
(8) Sawicki, *J. Am. Chem. Soc.*, **76**, 2269 (1954).

(9) Morris, Dubnik, Dunn, and Johnson, *Cancer Research*, **7**, 730 (1947).

(10) Melting points are uncorrected and were determined in a heated Thiele tube (containing coconut oil) unless otherwise stated.

(11) Ray, Argus, and Barth, *J. Org. Chem.*, **12**, 794 (1947).

TABLE II

ALKYL DERIVATIVES OF 2-THIOLFLUORENE AND 2-FLUORENESULFONAMIDE 

X	M.P., °C.	Formula	Analyses: Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
Methylthio[a]	135–136	$C_{14}H_{12}S$	79.2	79.1	5.7	5.6
Ethylthio[a]	78–79	$C_{15}H_{14}S$	79.6	79.6	6.2	6.2
Benzylthio[a]	133–134	$C_{20}H_{16}S$	83.3	83.2	5.6	5.7
Cyclopentylthio[a,b]	94–95	$C_{18}H_{18}S$	81.2	81.3	6.8	6.8
Mesylthio[c]	167–169	$C_{14}H_{12}O_2S_2$	60.9	60.8	4.4	4.3
N-Ethylsulfonamide[d,e]	137–138	$C_{15}H_{15}NO_2S$	65.9	66.0	5.5	5.5
N,N-Diethylsulfonamide	111.0–111.5	$C_{17}H_{19}NO_2S$	67.8	67.8	6.3	6.5
N-Butylsulfonamide	132–133	$C_{17}H_{19}NO_2S$	67.8	67.7	6.3	6.4
N,N-Dibutylsulfonamide	129–130	$C_{21}H_{27}NO_2S$	70.6	70.7	7.6	7.5
N-Isopropylsulfonamide	171–172	$C_{16}H_{17}NO_2S$	66.9	66.9	5.9	5.9

[a] The alkylating agents for the preparation of these derivatives were methyl iodide, ethyl iodide, benzyl chloride, and cyclopentyl bromide. The latter chemical was donated by the Michigan Chemical Company, St. Louis, Michigan. [b] *Anal.* for S: Calc'd, 12.0. Found, 11.9. [c] The acylating agent was methane sulfonyl chloride. [d] The primary and secondary amines for the preparation of the sulfonamides were kindly donated by the Carbide and Carbon Chemicals Company. [e] *Anal.* for S: Calc'd, 11.7. Found, 11.8.

in 80 ml. of boiling ethanol was added 2 g. of potassium hydroxide in 10 ml. of methanol followed by 0.011 mole of the appropriate halide. The mixture was refluxed for one hour. Excess water was added and the precipitate was crystallized from aqueous methanol, aqueous acetic acid, or hexane. The data on these compounds are given in Table II. The yields ranged from 75–85%.

General procedure for the preparation of 2-fluorenesulfonamides. 2-Fluorenesulfonyl chloride[12] (2.65 g., 0.01 mole) was refluxed with 25–50 ml. of the appropriate primary or secondary amine for 30 minutes, cooled, and then poured into dilute sulfuric acid. Crystallization of the precipitates from hexane or heptane gave colorless crystals of the sulfonamides, the data of which are shown in Table I. Yields ranged from 65 to 80%.

2-Mesyloxyfluorene. A solution of 2-hydroxyfluorene[13] in benzene containing an equivalent weight of pyridine was reacted with an equivalent amount of methanesulfonyl chloride. The mixture was refluxed 5 minutes, water was added, and the benzene was removed by steam-distillation. The residue was crystallized from methanol to give a 40% yield of colorless crystals, m.p. 147–148°.

Anal. Calc'd for $C_{14}H_{12}O_3S$: C, 64.6; H, 4.6. Found: C, 64.5; H, 4.5.

2-Mesylaminofluorene. 2-Aminofluorene (9.1 g.) in 42 ml. of pyridine was reacted with 4.1 ml. of methanesulfonyl chloride. The mixture was refluxed for half an hour and then was added to excess water. Crystallization from ethanol gave 10.3 g. (80%) of glistening crystals, m.p. 206–207°.

Anal. Calc'd for $C_{14}H_{13}NO_2S$: C, 64.9; H, 5.0; N, 5.4. Found: C, 65.0; H, 5.0; N, 5.3.

2-Methylmesylaminofluorene. To a solution of 19 g. of 2-mesylaminofluorene and 4.4 g. of potassium hydroxide in 300 ml. of hot ethanol was added 6 ml. of methyl iodide. The mixture was refluxed for 3 hours. Excess water was added. Crystallization of the precipitate from ethanol gave 17 g. (85%) of colorless needles, m.p. 170–172°.

Anal. Calc'd for $C_{15}H_{15}NO_2S$: C, 65.9; H, 5.5; N, 5.1. Found: C, 65.7; H, 5.6; N, 5.0.

2-Mesylfluorene. A solution of 2.1 g. of 2-methylthiofluorene in 21 ml. of acetic acid containing 4.2 ml. of 30% hydrogen peroxide was refluxed for 2 hours. Then 20 ml. of water was added. The mixture was boiled several minutes and allowed to cool. The yellowish crystals were crystallized from aqueous acetic acid to give 2 g. (82%) of colorless crystals, m.p. 152.5–153.5°.

Anal. Calc'd for $C_{14}H_{12}O_2S$: S, 13.1. Found: S, 13.0.

2-Mesyl-9-fluorenone. To a gently refluxing solution of 2.44 g. of 2-mesylfluorene in 20 ml. of acetic acid was gradually added 5 g. of powdered chromium trioxide. The mixture was gently refluxed an additional hour and then was poured into excess dilute sulfuric acid. Crystallization from acetic acid gave 1.55 g. (60%) of glistening yellow plates, m.p. 239–240°.

Anal. Calc'd for $C_{14}H_{10}O_3S$: C, 65.1; H, 3.9; S, 12.4. Found: C, 65.1; H, 4.0; S, 12.2.

2-Mesyl-7-nitrofluorene. Finely powdered 2-mesylfluorene (2.44 g.) was added in small amounts to a stirred mixture of 10 ml. of acetic acid and 10.6 ml. of fuming nitric acid (*d.* 1.5) at room temperature. The mixture was warmed to 70° and then was allowed to cool to room temperature over several hours. Excess water was added. The precipitate was crystallized from acetic acid to give 1.2 g. (42%) of faintly yellow needles, m.p. 299–300° dec. (placed in block at 295°).

Anal. Calc'd for $C_{14}H_{11}NO_4S$: S, 11.1; N, 4.84. Found: S, 10.8; N, 5.0.

2-Mesyl-5-nitrofluorene. The acetic acid mother liquor from the crystallization of 2-mesyl-7-nitrofluorene was evaporated to one-fourth the volume and poured into excess water. The crude product (1.1 g., 38%) melted at 185–190°. Several crystallizations from benzene, aqueous acetic acid, and methanol gave a small amount of almost colorless needles, m.p. 197–199°.

Anal. Calc'd for $C_{14}H_{11}NO_4S$: C, 58.1; H, 3.81; N, 4.84. Found: C, 58.2; H, 3.95; N, 4.78.

2-Mesyl-7-aminofluorene. Finely powdered 2-mesyl-7-nitrofluorene (2.43 g.) was suspended in 60 ml. of boiling ethanol. Anhydrous calcium chloride (0.7 g.) in 13 ml. of water and 21 g. of zinc dust were added. The mixture was vigorously refluxed for 2 hours, cooled, and filtered. The residue was extracted with boiling Methyl Cellosolve. The combined solutions were added to excess water. Crystallization from ethanol gave 2 g. (92%) of colorless crystals, m.p. 231–232° dec. (placed in bath at 225°). The compound has a blue fluorescence in alcoholic solution.

Anal. Calc'd for $C_{14}H_{13}NO_2S$: C, 64.9; H, 5.02; N, 5.41. Found: C, 64.7; H, 5.12; N, 5.36.

2-Mesyl-7-acetylaminofluorene. 2-Mesyl-7-aminofluorene in xylene solution was refluxed with acetic anhydride for 20 minutes. Crystallization of the precipitate from alcohol gave a 90% yield of yellowish needles, m.p. 269–270°.

Anal. Calc'd for $C_{16}H_{15}NO_3S$: C, 63.8; H, 4.98; N, 4.65. Found: C, 63.8; H, 5.08; N, 4.61.

Ultraviolet absorption spectra. All spectra were determined in 95% ethanol on a Beckman Model DU spectrophotometer.

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(12) Courtot, *Ann.*, [10] **14**, 5 (1930).

(13) Ruiz, *Anales asoc. quim. argentina*, **16**, 170 (1928).