

dropwise during 5 min. with constant stirring. The mixture was stirred for 30 min., and the orange solid was collected, washed with two 50-ml. portions of benzene, and dried *in vacuo*. About 5.5 Gm. of product was obtained, m.p. 170–172°. $\nu_{\text{min}}^{\text{Nujol}}$ 960, 980, 1040, 1135, 1200, 1540, 1650.

Anal.—Calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{S}_2$: C, 53.39; H, 5.52; N, 19.16; S, 21.93. Found: C, 53.08; H, 5.59; N, 19.32; S, 21.10.

4-Pyridylmethylammonium N-4-Pyridylmethyl-dithiocarbamate—4-Aminomethylpyridine (11 Gm., 0.1 mole) (Reilly Tar and Chemical Corp.) in 30 ml. of absolute ethanol was ice-cooled and stirred while 3.5 ml. (0.05 mole) of carbon disulfide was added dropwise. The mixture was stirred for 15 min. and the solid was collected and washed with two 25-ml. portions of absolute ethanol. About 12 Gm. (80.5%) of a white, light-sensitive solid was obtained, m.p. 131–132°. $\nu_{\text{KB}}^{\text{min}}$ 940, 1000, 1070, 1115, 1225, 1300, 1600.

Anal.—Calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{S}_2$: C, 53.39; H, 5.52; N, 19.16; S, 21.93. Found: C, 53.19; H, 5.58; N, 18.70; S, 21.87.

3-Pyridylmethylammonium N-3-Pyridylmethyl-dithiocarbamate—The same procedure was used as above. From 3-aminomethylpyridine (11 Gm., 0.1 mole) was obtained 13.8 Gm. (92.6%) of a white solid that melted at 130–132°. $\nu_{\text{KB}}^{\text{min}}$ 920, 975, 1050, 1185, 1250, 1300, 1575.

Anal.—Calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{S}_2$: C, 53.39; H, 5.52; N, 19.16; S, 21.93. Found: C, 53.19; H, 5.27; N, 18.55; S, 21.89.

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Keyphrases

Antiradiation compounds
 Pyridine dithiocarbamates—synthesis
 Pyrimidine dithiocarbamates—synthesis
 IR spectrophotometry—structure
 Radiation protective properties

New Compounds: Fluorene Derivatives as Potential Carcinogens

By NELLIE W. PITZER and FRANCIS E. RAY*

A series of eight new *N*-substituted fluorenylamides have been synthesized for evaluation of carcinogenic activity.

IT HAS BEEN reported that diethylnitrosamine produces hepatic carcinomas in rats (1, 2). Since *N*-2-fluorenylamine is also a carcinogen (3), it was thought that *N*-2-fluorenylethyl nitrosamine (I) might have a similar or stronger activity.

Because *N*-2-fluorenylsuccinamic acid is a potent carcinogen (4), additional derivatives (II, III, IV, V and VI) were synthesized. Since nicotinic acid is known to be involved in the biological oxidation systems (5), carcinogenic activity might be found in *N*-2-fluorenylnicotinamide (VII). In the generally less carcinogenic fluorenone series, *N,N',N''*-2,4,7-fluorenylene(9-acetoxy)trisacetamide (VIII) was obtained.¹

Received July 26, 1967, from the Pharmaceutical Chemistry Research Laboratory, University of Florida, Gainesville, FL 32601.

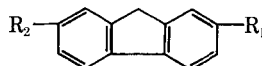
Accepted for publication September 12, 1967.

This investigation was supported by research grant RO1 CA 07737 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

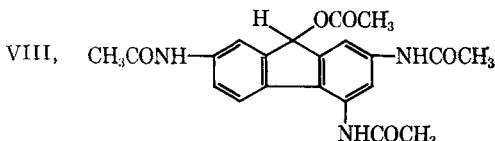
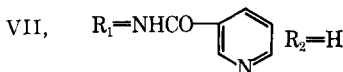
The authors thank Dr. Danuta Malejka for her assistance in preparing this manuscript.

* Deceased.

¹ Compounds I, II, III, and VIII were proved to be carcinogenic in the preliminary investigation by Dr. Harold P. Morris, National Cancer Institute, Bethesda, Md. All compounds are subject of further studies in this institute.



- I, $\text{R}_1 = \text{N} \cdot (\text{NO})\text{CH}_2\text{CH}_3$, $\text{R}_2 = \text{H}$
 II, $\text{R}_1 = \text{NHCOCH}_2\text{CH}_2\text{COOH}$, $\text{R}_2 = \text{NHCOCH}_2\text{CH}_2\text{COOH}$
 III, $\text{R}_1 = \text{NHCOCH}_2\text{C} : (\text{CH}_2)\text{COOH}$, $\text{R}_2 = \text{H}$
 or $\text{R}_1 = \text{NHCO} : (\text{CH}_2)\text{CH}_2\text{COOH}$ (Structural studies on this compound will be presented in a future communication.)
 IV, $\text{R}_1 = \text{NHCO}(\text{CH}_2)_6\text{CH}_3$, $\text{R}_2 = \text{H}$
 V, $\text{R}_1 = \text{NHCO}(\text{CH}_2)_6\text{CH}_3$, $\text{R}_2 = \text{NHCO}(\text{CH}_2)_6\text{CH}_3$
 VI, $\text{R}_1 = \text{NHCO}(\text{CH}_2)_{14}\text{CH}_3$, $\text{R}_2 = \text{H}$



EXPERIMENTAL

Ultraviolet spectra were obtained on a Hitachi Perkin-Elmer 139 UV-VIS spectrophotometer in 95% ethanol. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories.

N-2-Fluorenylethyl nitrosamine (I)—*N*-2-Fluorenylethylamine (6) (6 Gm., 0.03 mole) was heated in 300 ml. of water until the solid melted; 20 ml. of hydrochloric acid was added, and the mixture was cooled to 0–4°. Sodium nitrite (3.5 Gm. in water), 200 ml. of water, and 100 ml. of ether were added. With stirring, more ether was added. The aqueous and ether layers were separated, and the aqueous layer was extracted with ether. The combined ether extracts were washed with water, 10% sodium bicarbonate, and water; dried over sodium carbonate and evaporated *in vacuo*. The yellow product (I) was washed with pentane and dried. Yield, 1.7 Gm. (25%); m.p., 129–134°. Recrystallization from 250 ml. hexane gave 1.3 Gm., m.p. 132–134°. $\lambda_{\max.}$, $\mu\mu$ 266–268 (ϵ 13,000), 304–307 (ϵ 18,000).

Anal.—Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.70; H, 5.86; N, 11.66.

***N,N'*-2,7-Fluorenylenebis-succinamic Acid (II)**—To a solution of 20 Gm. (0.1 mole) of *N,N'*-2,7-fluorenylenediamine in 50 ml. of pyridine was added 22 Gm. (0.22 mole) of succinic anhydride, and the mixture was heated with stirring. The precipitate was filtered, washed successively with pyridine and ethanol, and dried. The solid was heated in 0.2 *N* NaOH with charcoal, the solution was filtered hot, and acidified with HCl. The white precipitate (II) was filtered, washed with water, stirred 15 min. in glacial acetic acid, filtered, washed, and dried. Yield, 20 Gm. (55%); m.p. 251–260°. A sample for analysis was dissolved in pyridine, precipitated with hexane, collected, and extracted with toluene, m.p. 256–257°; $\lambda_{\max.}$, $\mu\mu$ 303–304, 312–315 sh, 320–322 sh.

Anal.—Calcd. for $C_{21}H_{20}N_2O_6$: C, 63.63; H, 5.09; N, 7.07. Found: C, 63.71; H, 5.02; N, 7.02.

***N*-2-Fluorenylitaconamic Acid (III)**²—To a solution of 4.6 Gm. (0.025 mole) of *N*-2-fluorenylamine in 50 ml. of chloroform at 50–55° was added rapidly a solution of 2.8 Gm. (0.025 mole) of itaconic anhydride also at 50–55°, to obtain a white precipitate, 6.8 Gm. (93%); m.p. 207–208°. Recrystallization from ethanol gave a m.p. 219°. $\lambda_{\max.}$, $\mu\mu$ 289–292 (ϵ 28,600), 300–302 sh (ϵ 20,700), 314.5 (15,800).

Anal.—Calcd. for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.63; H, 5.12; N, 4.88.

***N*-2-Fluorenyloctanoylamide (IV)**—To a solution of 4.5 Gm. (0.035 mole) of *N*-2-fluorenylamine in 350 ml. of dry benzene was added 5.5 ml. of octanoyl chloride, and the mixture was refluxed 5–6 hr. The white precipitate was filtered and washed with hexane. Yield, 5.4 Gm. (91%); m.p. 157–160°. Recrystallization from ethanol gave a m.p. 160–161°. $\lambda_{\max.}$, $\mu\mu$ 289 (45,600), 303 (34,300), 314 (28,900).

Anal.—Calcd. for $C_{21}H_{22}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.15; H, 8.20; N, 4.68.

***N,N'*-2,7-Fluorenylenebis-octanoylamide (V)**—To a suspension of 10 Gm. (0.05 mole) of *N,N'*-2,7-fluorenylenediamine in 200 ml. of dry benzene was added 18 ml. of octanoyl chloride, and the mixture was refluxed 2 hr. Yield, 18 Gm. (74%); m.p. 238–246°. Recrystallization from dimethylformamide gave a m.p. of 254°. $\lambda_{\max.}$, $\mu\mu$ 304 (ϵ 53,000), 320–322 sh (ϵ 44,400).

² Prepared by Miss Sandra Rose in this laboratory.

Anal.—Calcd. for $C_{29}H_{40}N_2O_2$: C, 77.63; H, 8.99; N, 6.24. Found: C, 77.62; H, 9.20; N, 6.06.

***N*-2-Fluorenylpalmitoylamide (VI)**—To a solution of 9 Gm. (0.05 mole) of *N*-2-fluorenylamine in 500 ml. of dry benzene was added 15.5 ml. of palmitoyl chloride and the mixture was refluxed 2 hr. to give a white precipitate. Yield, 16 Gm. (76%); m.p. 148–151°. Recrystallization from ethanol gave a m.p. of 150–151°. $\lambda_{\max.}$, $\mu\mu$ 289 (ϵ 36,100), 314 (ϵ 19,600).

Anal.—Calcd. for $C_{29}H_{41}NO$: C, 82.99; H, 9.85; N, 3.34. Found: C, 82.78; H, 9.69; N, 3.50.

***N*-2-Fluorenylnicotinamide (VII)**³—To 12 Gm. (0.08 mole) of nicotinoyl chloride was added a solution of 18 Gm. (0.14 mole) of *N*-2-fluorenylamine in 125 ml. of dry benzene alternately with 21 Gm. of Na_2CO_3 . The thick mixture was refluxed 1 hr., filtered, and washed with benzene. The dried cake was broken up and, in 30-Gm. portions, was stirred and heated in water for 20 min. Yield, 20 Gm. (70%). Recrystallized from ethanol, the m.p. was 203–205°; $\lambda_{\max.}$, $\mu\mu$ 268–278 sh (ϵ 16,800), 314–316 (ϵ 25,700).

Anal.—Calcd. for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.66; H, 4.89; N, 9.80.

***N,N',N''*-2,4,7-Fluorenylene-(9-acetoxy)-tris-acetamide (VIII)**—2,4,7-Trinitrofluorenone (5.25 Gm. 0.017 mole) in 125 ml. of glacial acetic acid was heated in a pressure bottle, 0.06 Gm. PtO_2 was added, and the hot mixture was placed quickly on the Parr pressure reaction apparatus. Hydrogen was added at 40 p.s.i. The pressure dropped to 25.5 p.s.i. in 20 min. The reaction mixture was filtered into 20 ml. of acetic anhydride and left for 1 hr. It was heated 2 hr., the volume was reduced, and the mixture was allowed to stand overnight. The dark red precipitate was filtered, washed with acetic acid and then benzene, and extracted with hot ethanol. Yield, 3.5 Gm. (52%); m.p. over 400°. It was recrystallized from dimethylformamide: $\lambda_{\max.}$, $\mu\mu$ 286 (ϵ 31,100).

Anal.—Calcd. for $C_{21}H_{21}N_3O_5$: C, 63.79; H, 5.35; N, 10.63. Found: C, 64.33; H, 5.12; N, 10.39.

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³ Prepared by Mrs. Margaret B. Stone in this laboratory.



Keyphrases

Fluorene derivatives
N-fluorenamides—synthesis
 UV spectrophotometry—structure