[Contribution from the Chemistry Research Laboratory, Department of Surgery,
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Derivatives of Fluorene. II. 9-Arylimino Compounds[1]

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Thirty-two new azomethine derivatives of fluorene have been prepared. Several catalysts not used previously for the preparation of azomethines are reported.

Several series of fluorene compounds containing one or two azomethine groups have been prepared. The compounds, related to known carcinogenic derivatives of fluorene, are of potential biological interest. One of them has shown borderline activity in preliminary tests for inhibition of Sarcoma 180 in mice.[2]

Starting with variously substituted fluorenones and the appropriate arylamines, we have prepared compounds using as catalysts zinc chloride[3,4] aluminum chloride, acetic acid, phenol, trifluoroacetic acid, or phosphonic acid ion exchange resin.[5] The choice of the particular catalyst was dictated by the yield and ease of purification of the product.

Each of the catalysts used appeared to have an optimum temperature range. Highest yields were obtained with zinc chloride between 160–190°; with aluminum chloride, between 120–130° (above 130°, the formation of tars increased). In the case of acetic acid or phenol, best results were obtained at reflux temperatures.

During the course of the preparation of the phenylimino-nitro derivatives, it was found that, when the molar ratio of aniline to nitroketone was less than 2:1, the yield was essentially the same, but the product was difficult to purify. The same effect was found when the ratio of zinc chloride to ketone was greater than 1 g.:0.1 mole.

The phenylimino and *p*-fluorophenylimino compounds are all moderately to extremely soluble in chloroform and thus were readily separated from the Lewis acid amine salt. With the exceptions of N-(2-methylaminofluorenylidene)aniline (VIII) and N-(2-trifluoroacetamidofluorenylidene)aniline (X), all crystallized readily from chloroform, absolute ethanol, or carbon tetrachloride. VIII crystallized from chloroform-carbon tetrachloride after standing in the refrigerator for one month. X appeared to decompose slightly on recrystallization.

The bisnitrofluorenylidene compounds of *p*-phenylenediamine and benzidine are insoluble in the common organic solvents. In order to purify them, they were extracted with solvents in which unreacted starting materials were soluble. Thus acetic acid and phenol were used in many of these preparations because they served both as solvent and catalyst, and were easily removed from the product. N,N′-Di-(2,7-dinitrofluorenylidene)-*p*-phenylenediamine could be crystallized from *o*-nitrotoluene; a red-colored addition compound crystallized out which decomposed at 113–114° to a golden-colored azomethine and *o*-nitrotoluene. The weight loss corresponded to a ratio of one N,N′-di-(2,7-dinitrofluorenylidene)-*p*-phenylenediamine to two *o*-nitrotoluene molecules.

The reaction time appears to affect the yield of product regardless of whether zinc chloride, aluminum chloride, or acetic acid is used. When aluminum chloride and zinc chloride are the catalysts, tar formation increases if the fusion time is much greater than one hour. When glacial acetic acid is used, the product forms quickly, but prolonged reflux splits the imine yielding ketone and acetylated amine. This is illustrated by four preparations of N,N′ - difluorenylidene - *p* - phenylenediamine. All conditions were kept constant except the reflux time. At 10 minutes, a 70% yield of product was obtained; at 30 minutes, a 60% yield; at 60 minutes, 42%; and at 180 minutes, 1.0%.

The reaction of benzidine with fluorenone in the presence of zinc chloride yielded two products. One was the same as that obtained when glacial acetic acid was the catalyst (XXXII). The other product was a yellow solid, m.p. 117–118° uncorr. The compound reacted with bi-indan-1,3-dione ("bindone")[6,7] to give a red-purple solution whereas N - fluorenylideneaniline and N,N′ - difluorenylidenebenzidine gave no color. The test with "bindone" indicated that a free amine group was present in the molecule. An attempt is being made to identify the compound.

When 2,5-dinitrofluorenone was condensed with either aniline or *p*-fluoroaniline, two compounds resulted. The reactions yielded a mixture of red and

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[2] Private communication from Division of Chemotherapy, Sloan-Kettering Institute.

[3] Reddelien, *Ber.*, **43**, 2476 (1910).

[4] Reddelien, *Ann.*, **388**, 165, 190 (1912).

[5] Duolite C-60, a phosphonic acid type resin, generously supplied by the Chemical Process Company, Redwood, California.

[6] Ionescu, *Ber.*, **60**, 1229 (1927).

[7] Wanag, *Ber.*, **69**, 189 (1936).

TABLE I

9-ARYLIMINOFLUORENE DERIVATIVES

FLUORENYLIDENE ANILINE COMPOUNDS

Compound No.	Ketone	Catalyst	t, min.	T, °C.	Yield, %	M.p., °C.	Crystal Color and Form	Crystallized from[l]	Formula	Analyses					
											Calc'd			Found	
										C	H	N	C	H	N
I	Fluorenone	Zinc chloride	45	183–185	81	88–89[h]	Deep yellow rods	Ethanol	—	—	—	—	—	—	—
II	2-Nitrofluorenone[a]	Aluminum chloride	15	125–130	73	142–143[i]	Golden plates	Chloroform	$C_{19}H_{12}N_2O_2$	75.99	4.03	9.33	75.97	4.04	9.32
III	2,7-Dinitro-fluorenone[b]	Zinc chloride	45	177–183	62	245.5–246.5	Orange rods	Chloroform	$C_{19}H_{11}N_3O_4$	66.08	3.21	12.17	66.08	3.20	12.05
IV	2,5-Dinitro fluorenone[b]	Zinc chloride	60	180–183	20	247.5–248.0	Yellow needles	Chloroform	$C_{19}H_{11}N_3O_4$	66.08	3.21	12.17	66.25	3.31	12.32
					53	211–212	Red rods	Chloroform	$C_{19}H_{11}N_3O_4$	—	—	12.17	—	—	11.88
V	2,4,7-Trinitro-fluorenone[c]	Zinc chloride	60	185–190	67	224–225	Reddish-orange plates	Chloroform	$C_{19}H_{10}N_4O_6$	58.47	2.58	14.36	58.44	2.52	14.36
VI	2-Acetamido-fluorenone[d]	Zinc chloride	45	183–190	66	223–224	Yellow needles	Chloroform	$C_{21}H_{16}N_2O$	80.75	5.16	8.97	80.62	4.95	9.06
VII	2-Benzamido-fluorenone[e]	Zinc chloride	50	190–195	85	238–239	Yellow needles	Chloroform	$C_{26}H_{18}N_2O$	83.40	4.85	7.48	83.22	4.92	7.61
VIII	2-N-Methylamino-fluorenone[f]	Zinc chloride	45	185–190	59	141–142	Bright red rods	Chloroform-carbon tetrachloride	$C_{20}H_{16}N_2$	—	—	9.85	—	—	9.55
IX	2-N,N-Dimethyl-aminofluorenone[f]	Zinc chloride	45	165–175	60	129–131	Red rods	Chloroform-carbon tetrachloride	$C_{21}H_{18}N_2$	—	—	9.39	—	—	9.49
X	Trifluoroacet-amidofluorenone[f]	Zinc chloride	30	185–190	89	195–205 (dec.)	Yellow needles	Chloroform	$C_{21}H_{13}F_3N_2O$	—	—	7.65	—	—	7.28
FLUORENYLIDENE p-FLUOROANILINE COMPOUNDS															
XI	Fluorenone	Zinc chloride	60	170–175	87	142–143	Yellow cottony needles	Ethanol	$C_{19}H_{12}FN$	83.50	4.43	5.13	83.75	4.30	5.32
XII	2-Nitrofluorenone	Zinc chloride	30	170–175	84	228–229	Golden cottony needles	Chloroform	$C_{19}H_{11}FN_2O_2$	—	—	8.80	—	—	8.97
XIII	2,7-Dinitro-fluorenone	Zinc chloride	45	175–180	87	272–273	Orange cottony needles	Chloroform	$C_{19}H_{10}FN_3O$	—	—	11.57	—	—	11.41
XIV	2,5-Dinitro-fluorenone	Zinc chloride	60	175–180	55	178–179	Yellow needles	Chloroform	$C_{19}H_{10}FN_3O_4$	—	—	11.57	—	—	11.45
					26	180–181	Red plates	Chloroform	$C_{19}H_{10}FN_3O_4$	—	—	11.57	—	—	11.50

TABLE 1 *Continued*

Compound No.	Ketone	Catalyst	t, min.	T, °C.	Yield, %	M.p., °C.	Crystal Color and Form	Crystallized from[l]	Formula	Analyses Calc'd			Analyses Found		
										C	H	N	C	H	N
XV	2,4,7-Trinitrofluorenone	Zinc chloride	70	190–195	87	232.5–233.5	Orange plates	Chloroform	$C_{19}H_9FN_4O_6$	—	—	13.72	—	—	13.65
XVI	2-Acetamidofluorenone	Zinc chloride	45	175–180	83	205–206	Yellow needles	Acetone	$C_{21}H_{15}FN_2O$	—	—	8.48	—	—	8.51
FLUORENYLIDENE *p*-ACETAMIDOANILINE COMPOUNDS															
XVII	Fluorenone	Aluminum chloride	15	125–135	90	250–251	Golden needles	Chloroform	$C_{21}H_{16}N_2O$	—	—	8.97	—	—	8.80
XVIII	2-Nitrofluorenone	Acetic acid	15	135–140	42	314–315	Orange plates	(Toluene)	$C_{21}H_{15}N_3O_3$	—	—	11.76	—	—	11.73
XIX	2-Acetamidofluorenone	Zinc chloride	45	175–185	89	253–254	Yellow needles	Ethanol	$C_{23}H_{19}N_3O_2$	—	—	11.38	—	—	11.25
FLUORENYLIDENE *p*-BIPHENYLAMINE COMPOUNDS															
XX	Fluorenone	Trifluoroacetic acid	90	190	60–65	193.5–194.0[j]	Yellow needles	Ethanol	$C_{25}H_{17}N$	—	—	4.23	—	—	4.33
XXI	2-Nitrofluorenone	Trifluoroacetic acid	90	190	50	210–211	Red plates	Benzene	$C_{25}H_{16}N_2O_2$	79.77	4.28	7.44	79.91	4.30	7.30
XXII	2,5-Dinitrofluorenone	Trifluoroacetic acid	90	190	70	200–201	Red plates	Benzene	$C_{25}H_{15}N_3O_4$	—	—	9.97	—	—	9.97
FLUORENYLIDENE *β*-NAPHTHYLAMINE COMPOUNDS															
XXIII	Fluorenone	Cation exchange resin	90	190	62	113.5–115.0 (uncorr.)	Yellow needles	Ethanol	$C_{23}H_{15}N$	—	—	4.59	—	—	4.68
XXIV	2-Nitrofluorenone	Zinc chloride	90	190	45	166–167	Brick-red needles	Benzene	$C_{23}H_{14}N_2O_2$	78.84	4.03	8.00	78.86	4.00	8.11
FLUORENYLIDENE *α*-NAPHTHYLAMINE COMPOUNDS															
XXV	Fluorenone	Zinc chloride	90	175	45–50	116–117 (uncorr.)	Yellow needles	Ethanol	$C_{23}H_{15}N$	—	—	4.59	—	—	4.62
DIFLUORENYLIDENE *p*-PHENYLENEDIAMINE															
XXVI	Fluorenone	Acetic acid	10	Reflux	70	293–294[k]	Red rods	Chloroform	$C_{32}H_{20}N_2$	—	—	6.48	—	—	6.44
XXVII	2-Nitrofluorenone	Acetic acid	20	Reflux	86	dec. >400	Gold powder	(Acetic acid and ethanol)	$C_{32}H_{18}N_4O_4$	—	—	10.72	—	—	10.41

TABLE I *Continued*

Compound No.	Ketone	Catalyst	t, min.	T, °C.	Yield, %	M.P., °C.	Crystal Color and Form	Crystallized from[l]	Formula	Analyses Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
XXVIII	2,7-Dinitrofluorenone	Acetic acid	10	Reflux	95	444–448, dec.	Gold powder	(Acetic acid)	$C_{32}H_{16}N_6O_8$	62.75	2.63	13.72	62.68	2.76	13.58
						444–448, dec.	Red plates (see text)	*o*-Nitrotoluene	—	—	—	—	—	—	—
XXIX	2,4,7-Trinitrofluorenone	Acetic acid	25	Reflux	85	404–405, dec.	Purple powder	(Ethanol and acetic acid)	$C_{32}H_{14}N_8O_{12}$	—	—	15.96	—	—	15.70
XXX	2-Acetamidofluorenone	Phenol	360	Reflux	71	378–380, dec.	Yellow needles	Nitrobenzene	$C_{36}H_{26}N_4O_2$	79.10	4.79	10.25	78.59	4.93	9.96
XXXI	2-Aminofluorenone[g]	Zinc chloride	15	190–195	69	304–305, dec.	Brick red powder	Nitrobenzene	$C_{32}H_{22}N_4$	83.09	4.79	12.11	82.91	4.86	11.88
						DIFLUORENYLIDENE BENZIDINE COMPOUNDS									
XXXII	Fluorenone	Acetic acid	30	Reflux	40	350–352, dec.	Brick-red needles	Chloroform	$C_{38}H_{24}N_2$	—	—	5.51	—	—	5.60
XXXIII	2-Nitrofluorenone	Acetic acid	20	Reflux	62	402–404, dec.	Orange powder	(Acetic acid and ethanol)	$C_{38}H_{22}N_4O_4$	—	—	9.36	—	—	9.56
XXXIV	2,7-Dinitrofluorenone	Acetic acid	30	Reflux	40	420–422, dec.	Purple powder	(Acetic acid and ethanol)	$C_{38}H_{20}N_6O_8$	—	—	12.21	—	—	12.20
XXXV	2,4,7-Trinitrofluorenone	Acetic acid	20	Reflux	75	390–391	Mauve powder	(Acetic acid and ethanol)	$C_{38}H_{18}N_8O_{12}$	—	—	14.40	—	—	14.42
XXXVI	2-Acetamidofluorenone	Phenol	20	Reflux	66	379–380, dec.	Yellow needles	Nitrobenzene	$C_{42}H_{30}N_4O_2$	—	—	9.00	—	—	8.95

The ketones used as reactants were prepared by the methods listed, [a] through [g]. [a] Diels, *Ber.*, **34,** 1764 (1901). [b] Morgan and Thomason, *J. Chem. Soc.*, 2694 (1926). [c] *Org. Syntheses*, Coll. Vol. **3,** 837 (1955). [d] Acetylation of 2-aminofluorenone with acetic anhydride in pyridine. [e] Eckert and Langecker, *J. prakt. Chem.*, 226, 263 (1928). [f] Fletcher, Taylor and Dahl, *J. Org. Chem.*, 20, 1024 (1955). [g] Modification of the method of Diels, *Ber.*, **34,** 1764 (1901) (see also footnote ref. *f.*, p. 1023). A solution of 22.5 g. (0.10 mole) of pulverized 2-nitrofluorenone, 156 g. of ammonium sulfide (12% H_2S content), and 500 ml. of 95% ethanol were gently refluxed for 2.5 hours and worked up in the usual manner. [h] Reported m.p. 89°, see ref. (3). [i] Reported m.p. 141°, Courtot and Petitcolas, *Compt. rend.*, **180,** 297 (1925). [j] Reported m.p. 186°, Reddelien, *Ber.*, **54,** 3121 (1921). [k] Reported m.p. 278°, see ref. (3). [l] Solvents in parentheses indicate that the hot solvent was used to extract impurities.

yellow needles that were separated by repeated crystallization from acetone, chloroform, and benzene. In both cases the products gave the correct elemental analysis for nitrogen. Further data concerning these phenomena will be reported in a subsequent publication.

EXPERIMENTAL[8]

The general procedure used for each catalyst is illustrated below.

Aluminum chloride. Preparation of N-(2-nitrofluorenylidene)aniline (II). A mixture of 11.2 g. (0.05 mole) of 2-nitrofluorenone, 10 ml. of freshly distilled aniline, and 0.2 g. of aluminum chloride was fused at 125 ± 5°. A melt formed that bubbled vigorously. The reaction was stopped 15 minutes after bubbling started. The melt crystallized when cool. It then was dissolved in a small amount of hot chloroform and was filtered. The filtrate was concentrated to *ca.* 30 ml. from which solids crystallized. The first crop was unreacted 2-nitrofluorenone. Successive crops were golden-colored plates which were recrystallized from chloroform-carbon tetrachloride solution, yielding 10.9 g. of product, m.p. 135–141°. Further recrystallization raised the m.p. to 142–143°.

Phenol. Preparation of N,N'-di-(2-acetamidofluorenylidene)benzidine (XXXVI). A mixture of 11.8 g. (0.05 mole) of 2-acetamidofluorenone, 3.9 g. (0.021 mole) of benzidine, and 9.4 g. (0.10 mole) of phenol was heated to gentle reflux. The reaction was stopped 20 minutes after reflux began. The solids from the reaction were crushed under ether and were collected on the filter. The product then was extracted with 150 ml. of boiling acetone, filtered, and dried, yielding 10.3 g. (79%) of yellow crystals, m.p. 377–378° (dec.). Crystallization from nitrobenzene followed by boiling acetone extraction gave 8.7 g. (66%) of bright yellow crystals, m.p. 379–380° (dec.).

Glacial acetic acid. Preparation of N,N'-difluorenylidene-p-phenylenediamine (XXVI). A solution of 11.0 g. (0.061 mole) of fluorenone and 3.0 g. (0.028 mole) of *p*-phenylenediamine in 25 cc. of glacial acetic acid was refluxed with mechanical stirring for 10 minutes. The reaction mixture was cooled, filtered, washed twice with 50 ml. of glacial acetic acid, and dried, yielding 6.7 g. of product. Evaporation of the filtrate to dryness and extraction with hot ethanol yielded a further 2.2 g., which was combined and crystallized from chloroform yielding 8.5 g. (70%) of red crystals, m.p. 293–294°.

Trifluoroacetic acid or cation exchange resin.[5] The molar ratio of catalyst to ketone to amine was 1:10:11.1. The work-up of the product using the appropriate solvent was the same as for the fusion reaction above.

Zinc chloride. The method used was that of Reddelien.[3]

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(8) All melting points below 320° are corrected. Melting points below 300° were taken on a Fisher-Johns block; over 300°, they were taken in a capillary in an aluminum block. Some microanalyses were done by W. Manser, Herrliberg (Zch), Switzerland; some, by the Schwarzkopf Microanalytical Laboratory, Woodside 77, New York, and others, by one of us (M.E.T.).