TABLE II

PREPARATION OF N-SUBSTITUTED DIBROMO- AND DICHLOROMALEIMIDES

N-Substituent	Yield, %	M.P.	Formula	Carbon, %		Hydrogen, %		Chlorine, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_2CH_2OH	75	100–101	$C_6H_5Cl_2NO_3$	34.29	34.22	2.40	2.51	33.78	33.86
C_6H_5	87	204–206	$C_{10}H_5Cl_2NO_2$	49.59	49.96	2.13	2.26	29.30	29.47
C_6H_5	80	166–168	$C_{10}H_5Br_2NO_2$	36.25	36.47	1.52	1.78	48.31[a]	48.62[a]
C_6H_{11}(cyclo)	70	140–142	$C_{10}H_{11}Cl_2NO_2$	48.39	48.91	4.47	4.53	28.60	28.46
C_6H_5Cl-4	85	191–194	$C_{10}H_4Cl_3NO_2$	43.41	43.55	1.46	1.87	38.49	38.07
$C_6H_3Cl_2$,3-4	93	206–208	$C_{10}H_3Cl_4NO_2$	38.60	38.79	0.97	1.13	45.62	45.82
$C_6H_4CH_3$-4	89	192–194	$C_{11}H_7Cl_2NO_2$	51.57	51.29	2.76	2.80	28.05	27.59
$C_6H_4OCH_3$-4	74	206–207	$C_{11}H_7Cl_2NO_3$	48.54	49.06	2.59	2.73	26.07	25.95
CH_2COOH	69	196–197	$C_6H_3Cl_2NO_4$	32.14	32.39	1.35	1.56	31.66	31.25
C_6H_4COOH-2	91	237–239	$C_{11}H_5Cl_2NO_4$	46.16	46.46	1.76	1.78	24.80	24.07
C_6H_4COOH-3	92	289–290	$C_{11}H_5Cl_2NO_4$	46.16	46.12	1.76	1.87	24.80	24.16
C_6H_4COOH-4	91	>305	$C_{11}H_5Cl_2NO_4$	46.16	45.96	1.76	1.93	24.80	24.35
C_6H_4-$COOC_2H_5$-4	77	197–200	$C_{13}H_9Cl_2NO_4$	49.68	49.52	2.89	2.83	22.58	22.58
C_6H_4-SO_2NH_2-4	94	>300	$C_{10}H_6Cl_2N_2O_4S$	37.38	37.87	1.88	2.02	22.09	21.91
NHC_6H_5[b]	80	173–175	$C_{10}H_6Cl_2N_2O_2$	46.69	46.68	2.35	2.32	27.60	27.43
$NHO_2SC_6H_4CH_3$-4	71	164–166	$C_{11}H_8Cl_2N_2O_4S$	39.39	39.24	2.41	2.68	21.16	21.02
C_6H_3Cl-2-$COOCH_3$-5	84	156–157	$C_{12}H_6Cl_3NO_4$	43.05	43.45	1.81	1.93	31.81	31.55
$C_6H_3CH_3$-2-$COOCH_3$-5	82	121–122	$C_{13}H_9Cl_2NO_4$	49.68	50.05	2.89	2.77	22.58	22.54

[a] Bromine analysis. [b] Maleimide structure based on infrared spectrum with carbonyl absorptions at 5.55 μ and 5.75 μ. Dichloro-N-phenylmaleimide had similar infrared spectrum.

details. The procedure used to prepare the N-substituted dihalomaleimides consisted in the addition of 0.1 mole of the amino compound in 25–30 ml. of glacial acetic acid to a solution of 0.1 mole of the dihalomaleic anhydride in 50–75 ml. of glacial acetic acid at room temperature. The temperature was gradually increased to reflux and the refluxing was continued for 15–30 min. In most cases the N-substituted dihalomaleimide separated in crystalline form during the reflux period or on cooling. Sometimes it is necessary to dilute the cooled reaction mixture with water to obtain the maleimide. All of the maleimides in Table II were converted to colored maleimide derivatives, representative examples of which are listed in Table I.

(9) Imperial Chemical Industries Ltd., Australia. Application 33,896 (1958).

WILMINGTON, DEL.

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON, SCHOOL OF MEDICINE]

Derivatives of Fluorene. XIV. N-(Ring)-Fluorenylmaleimides[1]

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A series of N-(ring)-fluorenylmaleamic acids and maleimides is reported and some sulfhydryl addition compounds with the latter. Substituents with differing electron withdrawing or donor properties, it is speculated, might lead to compounds with differing biological activities. N-2-(7-Fluorofluorenyl)isomaleimide was produced in equal quantity with the normal maleimide in a standard cyclization procedure. No other instance of isomaleimide formation was observed. Infrared and ultraviolet spectral data are included and discussed. Solutions of at least some of these substances are unstable in absolute ethanol.

N-Fluorenylmaleimides and the corresponding maleamic acids have not been described in the literature. In a program developing many series of fluorene derivatives which might have interesting biological properties, we have prepared a number of maleimides[2] and maleamic acids with electron donor or withdrawing groups in various positions on the molecule. It seemed likely that such changes would give a series of compounds with differences, for example, in ease of reaction with sulfhydryl compounds. Alteration of biological activity might thus result.[3]

In general, procedures were standard and yields excellent. Typical reactions are illustrated in the experimental section. Table I lists products and analyses. N-2-(7-Fluorofluorenyl)maleamic acid was cyclized in the usual way to yield approximately equal quantities of normal maleimide and isomale-

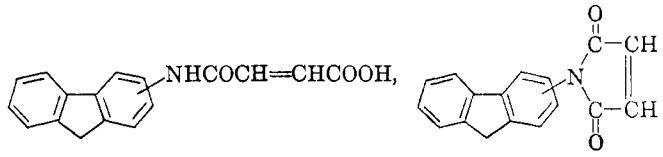
(1) This work was aided in part by a research grant (C-1744) from the National Cancer Institute, National Institutes of Health.

(2) A series of N-(9-fluorenyl)maleimides will be described shortly in a separate communication.

(3) Upon finding that injection of a small amount of N-ethylmaleimide, as suggested by its *in vitro* effect, suppresses gastric secretion in the Shay rat, we tried several other maleimides including N-2-fluorenylmaleimide. The latter was fully as depressant on a mole basis as N-ethylmaleimide: T. L. Fletcher, H. L. Buchman, A. W. Dahl, J. E. Jesseph, and H. N. Harkins, *J. Med. Pharm. Chem.*, 1, 275 (1959).

TABLE I

N-FLUORENYLMALEAMIC ACIDS AND *N*-FLUORENYLMALEIMIDES



R—	Yield, %	M.P.[a]	Formula	Calcd. C	Calcd. H	Calcd. N	Calcd. Br	Found[b] C	Found[b] H	Found[b] N	Found[b] Br
N-Fluorenylmaleamic Acids: R—NHCOCH=CHCOOH											
1-Fluorenyl	98.5	179.5–181.5 dec.	$C_{17}H_{13}NO_3$	73.11	4.69	5.02		72.75	4.78	5.08	
1-(9-Oxofluorenyl	100	203.5–205.5 dec.	$C_{17}H_{11}NO_4$	69.62	3.78	4.78		69.20	3.79	4.91	
2-Fluorenyl	97	220–228 dec.	$C_{17}H_{13}NO_3$	73.11	4.69	5.02		73.18	4.82	5.10	
2-(7-Acetamidofluorenyl)	100	218–220 dec.	$C_{19}H_{16}N_2O_4$			8.33				8.22	
2-(7-Bromofluorenyl)	99	230–235 dec.	$C_{17}H_{12}BrNO_3$			3.91	22.31			3.99	22.74
2-(9-Bromofluorenyl)	99–100	>300	$C_{17}H_{12}BrNO_3$	57.00	3.38	3.91		57.05	3.39	3.97	
2-(7-Fluorofluorenyl)	100	226–230 dec.	$C_{17}H_{12}FNO_3$	68.68	4.07	4.71		68.92	4.22	4.94	
2-(7-Nitrofluorenyl)	100	253–255 dec.	$C_{17}H_{12}N_2O_5$	62.96	3.73	8.64		62.44	3.72	8.36	
2-(3-Bromo-9-oxofluorenyl)	97	217–218.5 dec.	$C_{17}H_{10}BrNO_4$	54.86	2.71	3.76	21.47	54.89	2.95	3.79	21.86
2-(9-Hydroxyfluorenyl)	99	250–255 dec.	$C_{17}H_{13}NO_4$	69.14	4.44	4.74		69.35	4.54	4.75	
2-(9-Oxofluorenyl)	80	225–230 dec.	$C_{17}H_{11}NO_4$	69.62	3.78	4.78		69.73	3.92	5.54	
3-Fluorenyl	79	197–199.5 dec.	$C_{17}H_{13}NO_3$	73.11	4.69	5.02		73.01	4.70	5.41	
3-(9-Hydroxyfluorenyl)	88	191–193 dec.	$C_{17}H_{13}NO_4$	69.14	4.44	4.74		69.03	4.50	4.77	
3-(9-Oxofluorenyl)	77	187–192 dec.	$C_{17}H_{11}NO_4$	69.62	3.78	4.78		69.42	3.69	4.95	
4-Fluorenyl	84–95[c]	165.5–167 slight dec.	$C_{17}H_{13}NO_3$	73.11	4.69	5.02		73.13	4.66	5.20	
4-(9-Oxofluorenyl)	95	193–194.5 dec.	$C_{17}H_{11}NO_4$	69.62	3.78	4.78		69.88	4.04	4.89	
N-Fluorenylmaleimides: R—NCOCH=CHCO											
1-Fluorenyl	75	177–178	$C_{17}H_{11}NO_2$	78.15	4.24	5.36		78.54	4.34	5.20	
1-(9-Oxofluorenyl)	85	162.5–163.5	$C_{17}H_9NO_3$	74.18	3.30	5.09		74.26	3.31	5.16	
2-Fluorenyl	91	186.5–188	$C_{17}H_{11}NO_2$	78.15	4.24	5.36		78.14	4.32	5.04	
2-(7-Acetamidofluorenyl)	71	~286 (glassy melt)	$C_{19}H_{14}N_2O_3$	71.69	4.43			71.63	4.71		
2-(7-Bromofluorenyl)	81	204.5–205.5	$C_{17}H_{10}BrNO_2$	60.02	2.96	4.12	23.49	59.95	2.89	4.26	23.94
2-(9-Bromofluorenyl)	45	193–194 slight dec.	$C_{17}H_{10}BrNO_2$	60.02	2.96	4.12	23.49	60.19	2.85	3.85	23.72
2-(7-Fluorofluorenyl)[d]	43	244–245	$C_{17}H_{10}FNO_2$	73.11	3.71	5.02		73.42	3.75	5.32	
	50	145–146	$C_{17}H_{10}FNO_2$	73.11	3.61	5.02		73.03	3.54	5.23	
2-(7-Nitrofluorenyl)	85	>300	$C_{17}H_{10}N_2O_4$	66.66	3.29	9.15		66.83	3.45	9.22	
2-(3-Bromo-9-Oxofluorenyl)	100	234–234.5	$C_{17}H_8BrNO_3$	57.65	2.28	3.96	22.56	57.64	2.30	4.24	22.39
2-(9-Acetoxyfluorenyl)	88–92	219–220	$C_{19}H_{13}NO_4$	71.47	4.10	4.39		71.76	4.14	4.55	
2-(9-Oxofluorenyl)	82	223–224	$C_{17}H_9NO_3$	74.18	3.30	5.09		74.06	3.34	5.16	
3-Fluorenyl	77	182–183	$C_{17}H_{11}NO_2$	78.15	4.24	5.36		78.13	4.08	5.34	
3-(9-Oxofluorenyl)	100	201.5–202.5	$C_{17}H_9NO_3$	74.18	3.30	5.09		74.12	3.22	5.28	
4-(9-Oxofluorenyl)[e]	85	192–194	$C_{17}H_9NO_3$ As CH_3OH	70.35	4.26	4.56		70.76	4.79	4.50	

[a] Melting points were taken on a Fisher-Johns block and corrected to standards. [b] W. Manser, Herrliberg (Zch); Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and A. Bernhardt, Mülheim (Ruhr). [c] When the reaction was run at 50° for 1 hr., a 95% yield was obtained. [d] See Experimental. Calcd. for $C_{17}H_{10}FNO_2$: mol. wt. 279. Found: mol. wt. (high-melting isomer), 274; Mol. wt. (low-melting isomer), 274 (Rast). [e] This substance decomposed upon attempted purification and an analytical sample was not obtained.

imide. No other fluorenyl maleamic acid that we have examined, including *N*-2-(7-fluoro-9-oxofluorenyl)maleamic acid, appeared to give any isomaleimide. *N*-*p*-Fluorophenylmaleamic acid cyclized to one product, presumably the normal imide.

A few addition reactions with representative sulfhydryl compounds are included. We plan to report on these and similar reactions in more detail.

Table II gives the principal infrared bands, in potassium bromide, of both maleamic acids and maleimides, with proposed assignments. A lactone

(>C=O) band and a >C=N- band are found, as expected,[4] in the spectrum of 7-fluorofluorenyl isomaleimide. The formation of isomaleimides, as colorless substances, in the cyclization of *p*-alkoxyphenylmaleamic acids with acetyl chloride had been reported in the literature.[5] However, these colorless substances were later found to be α-chlorosuccinimides.[6] The formation of an isomaleimide was realized, for example, in the dehydration of *N*-(4-hydroxy-1-naphthyl)maleamic acid with trifluoroacetic anhydride,[4] with infrared spectrum as noted above.

(4) K. C. Tsou, R. J. Barrnett, and A. M. Seligman, *J. Am. Chem. Soc.*, **77**, 4613 (1955).

(5) A. Piutti, *Atti. reale accad. Lincei, Classe sci. fis. mat. e nat.*, [5] 18, II, 312 (1909); *Chem. Abstr.*, **4**, 2451 (1910).

(6) W. R. Roderick, *J. Am. Chem. Soc.*, **79**, 1710 (1957).

Upon recording the ultraviolet absorption spectra of a number of these maleimides in absolute ethanol, we found that, at least with some, there was a progressive change upon standing in alcohol. Warming accelerated the change (Table III). Solution in cyclohexane (where solubility permitted) gave a stable absorption curve, both after standing at room temperature and after warming. Upon replacement of most of the cyclohexane with alcohol (Table III) and further standing, the spectra showed progressive alteration with time. Reference 4 gives ultraviolet spectra, in 95% ethanol of *N*-ethylmaleimide and of naphthylmaleimides and related compounds. Since *N*-ethylmaleimide was on hand, we examined its spectrum in absolute ethanol. At a concentration of 10^{-4} mole/l., our figures are in good agreement with those reported, with the

TABLE II

INFRARED ABSORPTION DATA FOR *N*-FLUORENYLMALEAMIC ACIDS AND MALEIMIDES[a]

Compound	Cm.$^{-1}$: w(weak), m(medium), s(strong)	Compound	Cm.$^{-1}$: w(weak), m(medium), s(strong)
Maleamic Acids		Maleimides	
N-1-Fluorenyl-	3330(m), 3050(m), 1710(s), 1550(s), 1405(m), 850(s)	*N*-1-Fluorenyl-	3090(m), 1710(s), 1400(s), 1160(s), 840(s)
N-2-Fluorenyl-	3280(m), 3050(m), 1700(s), 1540(s), 1405(s), 850(s)	*N*-2-Fluorenyl-	3070(w), 1705(s), 1400(s), 1160(s), 823(s)
N-3-Fluorenyl-	3310(m), 3080(m), 1710(s), 1550(s), 1405(s), 850(s)	*N*-3-Fluorenyl-	3100(w), 1705(s), 1390(s), 1150(s), 838(s)
N-4-Fluorenyl-	3350(s), 3040(m), 1710(s), 1530(s), 1395(s), 843(s)	*N*-1-(9-Oxofluorenyl)-	3095(w), 1705(s), 1400(s), 1150(s), 830(s)
N-1-(9-Oxofluorenyl)-	3320(m), 3050(m), 1730(s), 1690(s), 1550(s), 1405(m), 840(s)	*N*-2-(9-Oxofluorenyl)-	3115(w), 1725(s), 1405(s), 1150(s), 836(s)
N-2-(9-Oxofluorenyl)-	3360(s), 3070(m), 1710(s), 1560(s), 1420(m), 847(s)	*N*-3-(9-Oxofluorenyl)-	3095(w), 1725(s), 1405(s), 1150(s), 831(s)
N-3-(9-Oxofluorenyl)-	3320(m), 3100(m), 1710(s), 1550(s), 1420(s), 853(s)	*N*-4-(9-Oxofluorenyl)- (As CH_3OH addition compound)	3280(s),[b] 3040(w), 1725(s), 1180(s), 1010(m), 822(m)
N-4-(9-Oxofluorenyl)-	3330(m), 3060(m), 1720(s), 1540(s), 1410(m), 850(m)	*N*-2-(7-Bromofluorenyl)-	3115(w), 1715(s), 1400(s), 1155(m), 830(m)
N-2-(7-Bromofluorenyl)-	3310(m), 3090(m), 1700(s), 1550(s), 1410(s), 852(s)	*N*-2-(9-Bromofluorenyl)-	3105(w), 1710(s), 1400(s), 1150(s), 828(s), 660(m)
N-2-(9-Bromofluorenyl)-	3310(m), 3080(m), 1710(s), 1550(s), 1410(m), 850(s), 644(m)	*N*-2-(7-Fluorofluorenyl)- (High-melting isomer)	3105(w), 1720(s), 1400(s), 1255(s), 1155(s), 1095(m), 826(s)
N-2-(7-Fluorofluorenyl)-	3300(m), 3110(m), 1700(s), 1540(s), 1410(s), 1260(s), 1095(w), 853(s)	(Low-melting isomer of above: *N*-2-(7-Fluorofluorenyl)- isomaleimide)	3075(m), 1790(s), 1715(s), 1680(s), 1400(m), 1260(s), 1085(s), 825(s)
N-2-(3-Bromo-9-oxofluorenyl)-	3310(s), 3050(m), 1715(s), 1540(s), 1400(s), 845(s), 640(m)	*N*-2-(3-Bromo-9-oxofluorenyl)-	3115(w), 1725(s), 1420(s), 1150(s), 827(s)
N-2-(9-Hydroxyfluorenyl)-	3320(s), 3090(m), 1710(s), 1550(s), 1410(m), 1315(m), 1030(m), 850(s)	*N*-2-(9-Acetoxyfluorenyl)-	3105(w), 1725(s), 1405(s), 1255(s), 1160(s), 835(s)
N-3-(9-Hydroxyfluorenyl)-	3310(s), 3105(m), 1710(s), 1540(s), 1410(m), 1310(m), 1010(m), 848(s)	*N*-2-(7-Nitrofluorenyl)-	3115(w), 1720(s), 1515(s), 1405(s), 1340(s), 1150(m), 829(s)

[a] Potassium bromide disks on a Beckman IR-5. The assignments of the absorption bands are as follows:

3360–3280	>N—H	1515, 1340	C—NO_2
1560–1530			
		1315, 1310, 1030, 1010	—OH band
3115–3040			
1420–1390	H H >C=C<		
855–822		1260–1255	Aryl-F (?)
		1095–1085	
1790–1690	>C=O	1255	—$OCOCH_3$
1680	>C=N—		
		1180–1150	—$N(C{=}O)_2$(?)
		660–628	—C(—Br)—

[b] —OH band.

TABLE III

ULTRAVIOLET ABSORPTION DATA OF CERTAIN MALEIMIDES[a]

Maleimide	Concn.[b]	Solution Conditions[c]	λ_{max} mμ	log ϵ_{max} (ϵ_{max})
N-Ethyl-[d]		Shaken in absolute ethanol at room temperature for 4 min.	217	4.13 (13,600)
			223[g]	4.07 (11,700)
			231[g]	3.75 (5600)
			297	2.87 (740)
	10^{-4} mole/l.	Shaken in absolute ethanol at room temperature for 4 min.	218	4.10 (12,600)
			223[g]	4.03 (10,600)
			231[g]	3.68 (4800)
			297	2.79 (620)
	10^{-4} mole/l.	Stood in absolute ethanol at room temperature for 24 hr.	217	4.07 (11,800)
			223[g]	3.99 (9800)
			231[g]	3.65 (4500)
			297	2.67 (470)
	10^{-4} mole/l.	Stood in absolute ethanol at room temperature for 24 hr. then heated on the steam bath for 0.5 hr.	217	4.02 (10,500)
			223[g]	3.94 (8800)
			231[g]	3.63 (4300)
			298	2.56 (360)
N-2-Fluorenyl-		Shaken in cyclohexane at room temperature for 25 min.	269	4.44
			274	4.44
			294	4.05
			305	4.07
		Stood in cyclohexane at room temperature for 1 hr. then heated at 60° for 0.5 hr.	269	4.45
			274	4.45
			294	4.06
			305	4.08
		Heated in absolute ethanol at 60° for 3 min.	268	4.29
			273[g]	4.28
			292[g]	4.02
			303	4.04
			315[g]	3.61
		Heated in absolute ethanol at 60° for 4 min. then stood at room temperature for ~1.5 hr.	272	4.23
			291[g]	4.10
			304	4.13
			316	4.10
		Heated in absolute ethanol at 60° for ~30 min. then stood at room temperature for ~3.5 hr.	273	4.15
			291[g]	4.10
			304	4.13
			316	4.10
N-2-(7-Fluorofluorenyl)-		Heated in absolute ethanol at 60° for 15 min. then stood at room temperature for 1 hr.	276	4.24
			307	4.22
			318	4.19
		Heated in absolute ethanol at 60° for 30 min. then stood at room temperature for 1 hr.	273	4.19
			308	4.16
			318	4.13
		Heated in absolute ethanol at 60° for 45 min. then stood at room temperature for 4 hr.	271	4.16
			307	4.09
			318	4.04
N-2-(7-Fluorofluorenyl)iso-		Shaken in cyclohexane at room temperature for 1 hr.	266	4.26
			297[g]	3.82
			307[g]	3.78
			373[g]	4.09
			391	4.17
			413[g]	4.06
		Shaken in cyclohexane at room temperature for 2.5 hr.	266	4.27
			297[g]	3.83
			307[g]	3.78
			373[g]	4.10
			391	4.18
			413[g]	4.07
		Shaken in cyclohexane at room temperature for 1 hr., the solution evaporated to one-quarter of its original volume and absolute ethanol added to make the original volume. This was then heated at 60° for 1 hr.	273	4.23
			307	4.15
			318	4.09
		Heated in absolute ethanol at 60° for 30 min. then stood at room temperature for 2.5 hr.	273	4.16
			307	4.14
			318	4.11

TABLE III (*Continued*)

Maleimide	Concn.[b]	Solution Conditions[c]	λ_{max} mμ	log ϵ_{max} (ϵ_{max})
		Heated in absolute ethanol at 60° for 30 min. then stood at room temperature for 3 hr.	273 308 319	4.16 4.14 4.12
		Heated in absolute ethanol at 60° for ~45 min. then stood at room temperature for ~4 hr.	273 308 318	4.10 4.08 4.06

[a] Determined with a Beckman DK-1 Recording Spectrophotometer. [b] 5×10^{-5} moles per liter unless indicated. [c] The temperature of the sample and reference cells was kept at 22–24°. [d] Obtained from Aldrich Chemical Co., Inc. Reported ultraviolet absorption data for this maleimide: λ_{max} 217 mμ (ε 12,740), 224 mμ (ε 10,750), 310 mμ (ε 510). See reference[4]. [e] Shoulder.

exception that we have a broad, low band at 297 mμ (reported, 310 mμ). After twenty-four hours in ethanol the absorption at all peaks had decreased moderately. After the latter solution had been heated for half an hour there was further decrease in absorption.

Upon evaporation of the alcoholic solutions of *N*-2-(7-fluorofluorenyl)maleimide and isomaleimide each gave a solid material different from the original (analytical) samples; a portion of this melted considerably lower than the original substance. It would appear that at least some of these maleimides in ethanol give spectra representing a mixture of maleimide and reaction product with ethanol. Additionally, the facts that the isomaleimide solution has pronounced color in cyclohexane and when first dissolved in alcohol(the color fades quickly in the latter), we feel that the 7-fluorofluorenylisomaleimide rather rapidly isomerizes. Its spectrum, after short contact with alcohol, is essentially the same as that of the 7-fluorfluorenyl maleimide (which, as pointed out, is probably that of a mixture).

Similarly, the spectrum of *N*-2-fluorenylmaleimide, taken in alcohol as soon as possible after solution, was very much like that in cyclohexane. This likewise altered upon further contact with ethanol. From the foregoing data it would appear that in our projected study of the relative reactivity of some of these maleimides with —SH compounds, ethanol should be avoided as a medium. Cyclohexane is a very poor solvent for many of the fluorenyl maleimides and we shall have to look further for a suitable solvent.

EXPERIMENTAL[7]

Fluorenamines were prepared as indicated: 1-fluorenamine,[8] 9-oxo-1-fluorenamine,[9] 2-fluorenamine,[10] 9-oxo-2-fluorenamine,[11] 9-hydroxy-2-fluorenamine,[12] 3-bromo-9-oxo-2-fluorenamine,[13] 7-fluoro-2-fluorenamine[10] (m.p. 135–136°, reported[14] m.p. 135–136°), 7-nitro-2-fluorenamine,[15] 9-oxo-3-fluorenamine,[16] 3-fluorenamine[17] (m.p. 152–153°, reported[18] m.p. 152–153°). Wolff-Kishner (Huang-Minlon) reduction of 9-oxo-4-fluorenamine[19] gave 4-fluorenamine (m.p. 114–115°, reported[20] m.p. 115–116°). 7-Acetamido- and 7-bromo-2-fluorenamine (m.p. 146–147°, reported[21] m.p. 146°), were obtained by reduction[10] of the corresponding nitro compounds. We were aided in the preparation of some of the starting materials by Mr. M. J. Namkung and by Misses K. N. Olsoe and B. J. Bigley.

All the *N*-fluorenylmaleamic acids were prepared by treating maleic anhydride with fluorenamines in a suitable solvent, such as methanol, acetone, or glacial acetic acid. The maleimides were made by cyclodehydration of the maleamic acids in acetic anhydride in the presence of fused sodium acetate.[19] Typical experiments follow.

N-2-Fluorenylmaleamic acid. To a mechanically stirred solution of maleic anhydride (35 g.) in anhydrous methanol (250 ml.), 2-aminofluorene (55 g.) dissolved in warm methanol (750 ml.) was added over a period of 30 min. The suspension was stirred at room temperature for 1 hr. and filtered. To the filtrate a second portion of maleic anhydride (17 g.) in methanol (50 ml.) was added. The mixture was warmed, stirred for 0.5 hr., and filtered. The combined precipitates, washed with methanol and dried, weighed 82 g.

N-2-Fluorenylmaleimide. A mixture of *N*-2-fluorenylmaleamic acid (75.7 g.), freshly fused sodium acetate (13.5 g.), and acetic anhydride (270 ml.) was heated with constant shaking on a steam bath for 30 min. After 1 hr. of standing at room temperature the reaction mixture was stirred into ice water and the precipitate was filtered, washed with sodium bicarbonate (5%) and water, and dried over phosphorus pentoxide giving 70 g. (99.5%) of the crude product. Recrystallization from chloroform-ethanol gave 64 g.

(7) See Table I, footnotes *a*, *b*.

(8) E. Sawicki and B. Chastain, *J. Org. Chem.*, **21**, 1028 (1956).

(9) J. W. Cook and J. S. Moffatt, *J. Chem. Soc.*, 1160 (1950).

(10) T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958).

(11) C. C. Arcus and M. M. Coombs, *J. Chem. Soc.*, 3977 (1954).

(12) H. L. Pan and T. L. Fletcher, *J. Org. Chem.*, **23**, 799 (1958).

(13) T. L. Fletcher and H. L. Pan, *J. Am. Chem. Soc.*, **78**, 4812 (1956).

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

(15) M. J. Namkung and T. L. Fletcher, *J. Org. Chem.*, **25**, 740 (1960).

(16) N. Ishikawa, M. Okazaki, and M. Hayashi, *Yûki Gôsei Kagaku Kyôkai-shi*, **16**, 34 (1958); *Chem. Abstr.*, **52**, 5349 (1958).

(17) Mr. M. J. Namkung improved preparation of this compound by Wolff-Kishner hydrolytic reduction of 3-acetamidofluorenone.

(18) E. K. Weisburger, *J. Am. Chem. Soc.*, **77**, 1914 (1955).

(19) E. H. Huntress, K. Pfister, 3rd., and K. H. T. Pfister, *J. Am. Chem. Soc.*, **64**, 2845 (1942).

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

(21) C. Courtot and C. Vignati, *Bull. Soc. Chim.*, **41**, 58 (1927).

N-2-(9-Hydroxyfluorenyl)maleamic acid. 2-Aminofluorenol[12] (7.9 g.) dissolved in boiling acetone (260 ml.) was added in small portions to a solution of maleic anhydride (5 g.) in the same solvent (5 min.) while the reaction mixture was stirred vigorously. The resulting suspension was continuously stirred for 1 hr. and filtered. The yellow solid was thoroughly washed with acetone and dried, 11.7 g.

N-2-(9-Acetoxyfluorenyl)maleimide. The foregoing maleamic acid (11.7 g.) was mixed with fused sodium acetate (1.5 g.) and acetic anhydride (80 ml.), heated on a steam bath for 15 min., then allowed to stand at room temperature for 30 min. The reaction mixture was stirred into 5% sodium bicarbonate solution and the yellow precipitate was filtered, washed thoroughly with dilute sodium bicarbonate and water, and dried, yielding 11.2 g. Recrystallization from benzene gave 8.8 g. (80%). A yield of 92% was obtained from a smaller batch.

N-2-(7-Acetamidofluorenyl)maleamic acid. 2-Acetamido-7-aminofluorene (22 g.) in glacial acetic acid (200 ml.) was added in a thin stream to a stirred (magnetic) solution of maleic anhydride (11 g.) in the same solvent (100 ml.) within 5 min. The reaction mixture was stirred for another 10 min., diluted with cold water, filtered, washed thoroughly with water, then twice with alcohol, and dried, 31 g.

N-2-(7-Acetamidofluorenyl)maleimide. A mixture of the above maleamic acid (15.6 g.), fused sodium acetate (2.4 g.), and acetic anhydride (120 ml.) was heated in a steam-cone for 40 min. with frequent shaking. The pasty reaction mixture was cooled, stirred into cold water, filtered, and washed with 5% sodium carbonate solution, followed by water, and dried, yielding 13.8 g. Recrystallization from chloroform-ethanol gave small needles, 10.5 g.

N-4-(9-Oxofluorenyl)maleimide. *N*-4-(9-Oxofluorenyl)-maleamic acid (4 g.), fused sodium acetate (0.8 g.), and acetic anhydride (25 ml.) were mixed, heated with constant shaking on a steam bath for 15 min., and cooled. The reaction mixture was stirred into 10% sodium acetate solution and the excess acetic anhydride destroyed with solid sodium bicarbonate. The product was filtered, washed, and dried. Recrystallization from methanol gave 3.2 g.

N-4-Fluorenylmaleamic acid. (a) 4-Fluorenamine (3.6 g., 0.02 mole) dissolved in warm glacial acetic acid (35 ml.) was gradually (10 min.) added to a stirred solution of maleic anhydride (2.2 g., 0.022 mole) in 15 ml. of glacial acetic acid. The solution was stirred for 2 more hr. and diluted with water. The yellow precipitate was filtered, washed with water followed by ethanol and dried, giving 4.7 g. (84%). Recrystallization from acetone-water gave an analytical sample.

(b) A mixture of 4-fluorenamine (5 g., 0.028 mole) and maleic anhydride (2.95 g., 0.03 mole) was dissolved in warm glacial acetic acid (50 ml.). The solution was stirred at 50° (bath) for 1 hr. then diluted with water. The product was isolated giving 7.4 g. (95%).

N-2-(7-Fluorofluorenyl)maleimide and N-2-(7-fluorofluorenyl)isomaleimide. *N*-2-(7-Fluorofluorenyl)maleamic acid (3 g., 0.01 mole), fused sodium acetate (0.5 g.), and acetic anhydride (10 ml.) were mixed and heated on a steam bath, with frequent shaking, for 15 min. After cooling to room temperature the pasty reaction mixture was stirred into 10% aqueous sodium acetate and the excess acetic anhydride destroyed with sodium bicarbonate solution (5%). The precipitate was filtered, washed, and dried giving 2.7 g., m.p. 145–235°.

Recrystallization from benzene gave orange needles, 1.2 g. (43%), m.p. 243.5–245°. A second recrystallization from benzene gave an analytical sample.

The low-melting orange isomaleimide was obtained from the benzene filtrates, 1.4 g. (50%), m.p. 144–145.5°. Several crystallizations from benzene-ligroin and acetone-ligroin gave an analytical sample.

N-2-(9-Bromofluorenyl)maleamic acid. A solution of maleic anhydride (1.1 g., 0.011 mole) in glacial acetic acid (60 ml.) was mixed with 9-bromo-2-fluorenamine hydrobromide[23] (3 g., 0.009 mole). The mixture was stirred and 0.9 g. of anhydrous sodium acetate was added in small portions. The reaction mixture was stirred for 30 min. then diluted with water. The product was filtered, washed with water, and dried giving 3.1 g. (99%), m.p. > 300°.

One crystallization from acetone gave an analytical sample.

3-Aminofluoren-9-ol. Sodium borohydride reduction[12] of 3-aminofluorenone gave 58% of the 9-ol, m.p. 146–147° slight dec.

Anal. Calcd. for $C_{13}H_{11}NO$; C, 79.16; H, 5.62; N, 7.10. Found: C, 79.15; H, 5.57; N, 7.05.

Sulfhydryl addition compounds:

N-2-Fluorenyl-α-S-[1'-(2'-acetamidonaphthyl)]mercaptosuccinimide. *N*-2-Fluorenylmaleimide (0.25 g.) and *N*-2-(1-thiolnaphthyl)acetamide (0.2 g., purchased from the Eastern Chem. Corp., Newark, N. J.) were each dissolved in about 40 ml. of hot ethanol and the mixture was boiled. In less than a minute the yellow color faded and a white precipitate came out. After boiling two more minutes the mixture was allowed to cool, filtered, washed with alcohol, and dried giving 0.45 g. of snow-white product, m.p. 250–251°. Recrystallization from glacial acetic acid did not raise the m.p.

Anal. Calcd. for $C_{29}H_{22}N_2O_3S$: C, 72.79; H, 4.63; N, 5.86; S, 6.69. Found: C, 72.96; H, 4.67; N, 6.10; S, 6.62.

N-2-Fluorenyl-α-S-n-hexadecylmercaptosuccinimide. A similar reaction for 30 min. in boiling acetone with cetyl mercaptan (Sapon Laboratories) gave a precipitate. The latter was taken up in chloroform and filtered through Whatman No. 2 paper which held a small amount of finely divided residue. Addition of ten volumes of methanol to the filtrate gave a light yellow precipitate. Centrifugation, methanol washing and drying gave 40%, m.p. ~105° (vitreous melt).

Anal. Calcd. for $C_{33}H_{45}NO_2S$: N, 2.70; S, 6.16. Found: N, 2.88; S, 6.15.

N-2-Fluorenyl-α-S-(2'-aminoethyl)mercaptosuccinimide. A mixture of 2-mercaptoethylamine hydrochloride, kindly provided by Evans Chemetics, Inc., New York City (0.25 g., 0.004 mole), and anhydrous sodium acetate (0.4 g.) was stirred into 10 ml. of acetone. Water was added dropwise until there was a homogeneous solution. To the magnetically stirred solution *N*-2-fluorenylmaleimide (0.5 g., 0.002 mole) in acetone (20 ml.) was added slowly over a period of 15 min. Stirring was continued for 30 min. and the mixture was cooled in the refrigerator and filtered, 0.3 g. (44%), m.p. 241.5–242.5°. Recrystallization from acetone gave an analytical sample, m.p. 243.5–244.5°. Another 0.15 g. (22%) of the addition compound was obtained from the acetone filtrate.

Anal. Calcd. for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; S, 9.48. Found: C, 67.82; H, 5.20; S, 9.26.

N-(2-(7-Fluorofluorenyl)-α-S-[1'-(2'-acetamidonaphthyl)]-mercaptosuccinimide. Equimolar *N*-2-(7-fluorofluorenyl)-maleimide, the high-melting isomer, and *N*-2-(α-thiolnaphthyl)acetamide were allowed to react in boiling acetone giving 90% of product, m.p. 257–258°.

Anal. Calcd. for $C_{29}H_{21}FN_2O_3S$: C, 70.15; H, 4.26; N, 5.64; S, 6.46. Found: C, 70.62; H, 3.99; N, 5.48; S, 6.12.

Addition compound of N-2-(7-fluorofluorenyl)isomaleimide and N-2-(α-thiolnaphthyl)acetamide. The addition compound of the low-melting isomer and *N*-(2-(α-thiolnaphthyl)acetamide was prepared in a similar manner, giving 80% of product, m.p. 255.5–256.5°. A mixture of this compound and the product obtained above melted at 250–256°.

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(22) N. E. Searle, U. S. Patent **2,444,536**; *Chem. Abstr.*, **42**, 7340 (1948).

(23) T. L. Fletcher and M. J. Namkung, *Derivatives of Fluorene. XII.* Submitted for publication.

Anal. Calcd. for $C_{29}H_{21}FN_2O_3S$: C, 70.15; H, 4.26; N, 5.64; S, 6.46. Found: C, 70.42; H, 4.24; N, 5.27; S, 6.07.

N-Phenyl-α-S-[1-(2-acetamidonaphthyl)]mercaptosuccinimide. *N*-Phenylmaleimide, m.p. 89.5–90° (reported m.p. 90–91°[22]), prepared in the usual manner from *N*-phenylmaleamic acid (kindly provided by the American Cyanamid Co.), was allowed to react with *N*-2-(α-thiolnaphthyl)-acetamide in acetone giving 83% of addition compound, m.p. 201.5–202.5°.

Anal. Calcd. for $C_{22}H_{18}N_2O_3S$: C, 67.67; H, 4.65; N, 7.18; S, 8.21. Found: C, 67.50; H, 4.63; N, 7.42; S, 8.54.

SEATTLE 5, WASH.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CLXIII.[1] Studies in Cyanosteroids. II.[2] The C_5-Cyano Analogs of Dihydrotestosterone and Dihydroprogesterone[3]

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The addition of hydrogen cyanide to testosterone and progesterone leads to complex reaction mixtures. Nitriles and amides, epimeric at C_5, are amongst the products obtained. Some transformations of 5α-cyanodihydroallotestosterone are discussed.

As a continuation of the studies from these laboratories of the effect of electronegative groups on the biological activity of steroid hormones[4] the preparation of some C_5- cyanosteroids was undertaken.

Although it has been known for several decades that α,β-unsaturated ketones undergo Michael type addition of hydrogen cyanide[5] it was not certain that nucleophilic attack by cyanide ion at the angular C_5 position of a steroidal Δ^4-3-ketone would occur readily. However, the reaction proceeded easily. Testerosterone acetate (Ib), for example, after treatment with an excess of potassium cyanide in 95% ethanol under reflux for five hours no longer displayed maximum absorption in ultraviolet at 240–242 m μ. Only the very low intensity absorption of an isolated carbonyl group could be detected. The product was divided into benzene soluble and insoluble fractions and chromatography of the former over neutral alumina gave two main fractions differing widely in their polarity toward alumina. Crystallization of the least polar fraction gave a nitrogen containing compound in an overall yield of 27% which had an analysis agreeing with $C_{20}H_{29}O_2N$ and which readily formed a mono acetate (IIb). It did not show any selective absorption in the ultraviolet other than a broad band at 276–292 mμ, ε 31. In the infrared (potassium bromide disk) it displayed bands at 3350 (−OH), 2240 (−CN) and 1720 cm.$^{-1}$ (>C=O). These data were clearly consistent with the product being 5-cyanodihydrotestosterone and the nitrile group was assigned the 5α-stereochemistry (IIa) when it was seen that its rotatory dispersion curve was only compatible with a *trans*- ring junction for rings A and B.[6] The mother liquors from the purification of IIa probably contained some of the 5β-epimer since the crude product direct from the chromatogram and prior to crystallization had $[\alpha]_{312.5}^{\text{dioxane}} + 350°$.[7]

However, fractional crystallization or careful chromatography of this mixture did not lead to any of the pure 5β-isomer.

The more polar products from the chromatogram were combined with the benzene insoluble fraction and acetylated with acetic anhydride and pyridine. Chromatography of the acetylated material afforded as the least polar product 5α-cyanodihydrotestosterone acetate (IIb) identical with the product obtained from 5α-cyanodihydrotestosterone (IIa). The second product was isomeric with IIb and in the infrared it exhibited bands at 2220, 1723 (broad), and 1250 cm.$^{-1}$ Its rotatory dispersion curve in dioxane solution displayed a negative Cotton effect. On the basis of these data it was formulated as 5β-cyanodihydrotestosterone acetate (III). The shapes of the rotatory dispersion curves (see Experimental section) are in agreement with the 5α- and 5β-stereochemistry assigned to II and III, respectively.[6]

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(1) Part CLXII, A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *Chem. & Ind. (London)*, 1299 (1960).

(2) Part I. A. Bowers, E. Denot, M. B. Sanchez, L. M. Sanchez-Hidalgo, and H. J. Ringold, *J. Am. Chem. Soc.*, 81, 5233 (1959).

(3) Through the courtesy of Dr. Carl Djerassi and Dr. Ken'ichi Takeda we learned that a similar investigation with cholestenone had been carried out in the Shionogi Laboratories; *cf.* W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, in press. We thank Dr. Takeda for a copy of this paper prior to publication.

(4) *Cf.* ref. (2) and references cited therein.

(5) *Cf.* C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, New York, 1953, p. 690. For some more recent examples *cf.* ref. (3), footnote 8.

(6) C. Djerassi, *Optical Rotatory Dispersion*, McGraw-Hill Book Co., Inc., New York, 1960, pp. 49–51.

(7) *Cf.* 5α-cyanodihydrotestosterone, $[\alpha]_{312.5}^{\text{dioxane}}$ +1147° and 5β-cyanodihydrotestosterone acetate $[\alpha]_{312.5}$ −484°.