# Derivatives of Fluorene. XVIII. New Halogenofluorenes. I. Potential Antitumor Agents[1,2]

HSI-LUNG PAN AND T. LLOYD FLETCHER

*Chemistry Research Laboratory of the Department of Surgery, University of Washington School of Medicine, Seattle 5, Washington*

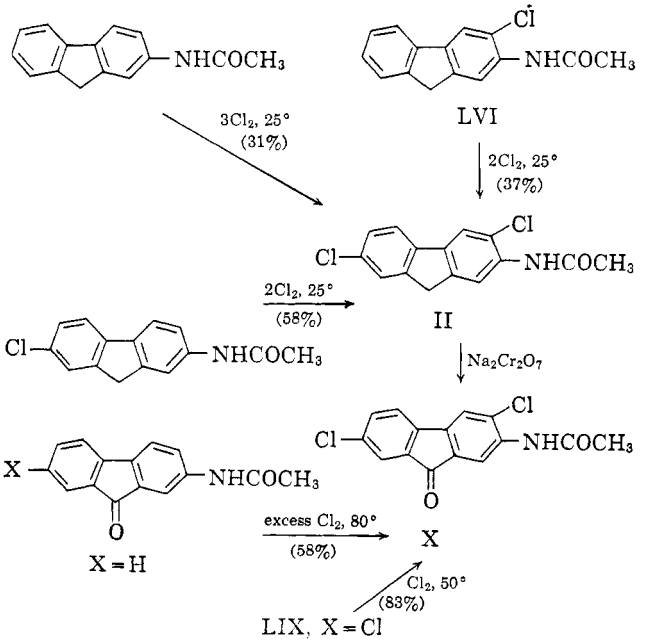
*Received August 8, 1963*

A number of new halogenofluorenes have been prepared and characterized. Chlorination of N-2-fluorenylacetamide and N-2-(9-oxofluorenyl)acetamide and some of their derivatives has been studied. With excess chlorine N-2-fluorenylacetamide and N-2-(7-chlorofluorenyl)acetamide give N-2-(1,3,4(?),7-tetrachlorofluorenyl)-acetamide[3] (I), whereas N-2-(6-chlorofluorenyl)- (LVII), and N-2-(6,7-dichlorofluorenyl)acetamide (LXVIII) give N-2-(1,3,4(?),6,7-pentachlorofluorenyl)acetamide (V). Monobromination or monochlorination of N-2-(9-oxofluorenyl)acetamide and its derivatives gives the 3-substituted halogenofluorenes exclusively. The antitumor activity of some of these compounds is reported; four have "specificity" at the 99.7% confidence level against Adenocarcinoma 755 (see Table III).

In a broad study of fluorene substitution reactions we have examined the chlorination of 2-acetamidofluorene (N-2-fluorenylacetamide) and some of its derivatives, and have prepared many new polyhalogenated fluorenes and elucidated their structure. These compounds were submitted to the Cancer Chemotherapy National Service Center and several have shown various degrees of antitumor activity in animals including four, thus far, with "specificity" at the 99.7% confidence level[4] against Adenocarcinona 755. The reason for such activity is obscure and we expect to extend this study to include analogous compounds in other ring systems.

Halogenation of fluorene and its derivatives has been studied by a number of investigators.[5] The 2-position in the unsubstituted fluorene molecule is the most readily halogenated site. Recently fluorene has been chlorinated by means of N,N-dichlorobenzenesulfonamide to give 2,7-dichlorofluorene and a trichlorofluorene (m.p. 126–127°)[6] of unspecified structure, which agrees with our 2,3,7-trichlorofluorene (LXXIII). Nitration of the former compound gave the 3-nitro derivative,[7] which was converted to a trichlorofluorene (m.p. 213–214°),[8] said to be the 2,3,7-isomer, by way of 3-amino-2,7-dichlorofluorene. We have chlorinated fluorene with three equivalents of chlorine in acetic acid, obtaining 2,7-dichlorofluorene as the main product with a small amount of 2,3,7-trichlorofluorene (LXXIII). Nitration of the former and oxidation gave 2,7-dichloro-3-nitro-9-oxofluorene[7] (we agree thus far with Kretov, *et al.*, as to melting point). Reduction gave us the amine (LIII) melting at 265–266° (lit.[7] m.p. 208–209°), but our N-acetyl derivative has the same melting point as that reported in the literature. We converted this to 9-oxo-2,3,7-trichlorofluorene (XXI) (m. p. 183.5–184°) (lit.[8] m.p. 265–266°). We cannot explain the discrepancy in melting points of LIII and XXI as compared with the literature, a discrepancy which arises three steps after the chlorination. We not only prepared XXI as just described, but also both by dichromate oxidation of 2,3,7-trichlorofluorene (m.p. 127.5–128.5°) (LXXIII), obtained as above but in higher yield with fluorene and a large excess of chlorine, and from 3-amino-2,7-dichlorofluorene through a Sandmeyer reaction and oxidation. Furthermore, our melting point for 3-amino-2,7-dichlorofluorene is the same as that reported by Kretov.

With an *ortho–para*-directing group, *e.g.*, amino or acetamido, situated at $C_2$, the substitution in the fluorene nucleus takes place readily at $C_3$ or $C_7$ and less readily at $C_1$ and other sites. Bromination of 2-amino-, 2-*p*-toluenesulfonamido-, and 2-acetamidofluorene with molecular bromine gave 1,3-dibromo-, 3,7-dibromo-, and 3-, 7-, or 1-monobromofluorene derivatives, depending on conditions.[5e] Monochlo-




(1) This work was supported, in part, by a grant (CA-01744) from the National Cancer Institute, National Institutes of Health, and, in part, by Research Career Development Award 5-K3-GM-14,991 to T. L. F.

(2) Previous paper in this series: *J. Org. Chem.*, **27**, 3639 (1962).

(3) Chlorine in the 4-position in this paper is designated as 4(?); although this is reasonably certain (as is discussed), it is not yet proved chemically.

(4) See Table III, footnote *d*.

(5) (a) A. Pictet and L. Ramseyer, *Ber.*, **44**, 2486 (1911); (b) A. Eckert and E. Langecker, *J. Prakt. Chem.*, **118**, 263 (1928); (c) C. Courtot, *Ann. Chim.*, **14**, 5 (1930); (d) J. Buffle, *Helv. Chim. Acta*, **15**, 1483 (1932); (e) F. Bell and D. B. Mulholland, *J. Chem. Soc.*, 2020 (1949); (f) N. Campbell and A. F. Temple, *ibid.*, 207 (1957); (g) G. H. Beaven, P. B. D. de la Mare, E. A. Johnson, and N. V. Klassen, *ibid.*, 988 (1962).

(6) A. E. Kretov and V. V. Litvinov, *Zh. Obshch. Khim.*, **31**, 1183 (1961); *Chem. Abstr.*, **55**, 23461 (1961).

(7) A. E. Kretov and V. V. Litvinov, *Zh. Obshch. Khim.*, **31**, 2585 (1961); *Chem. Abstr.*, **56**, 11511 (1962).

(8) A. E. Kretov and V. V. Litvinov, *Zh. Obshch. Khim.*, **32**, 3799 (1962); *Chem. Abstr.*, **58**, 12480 (1963).

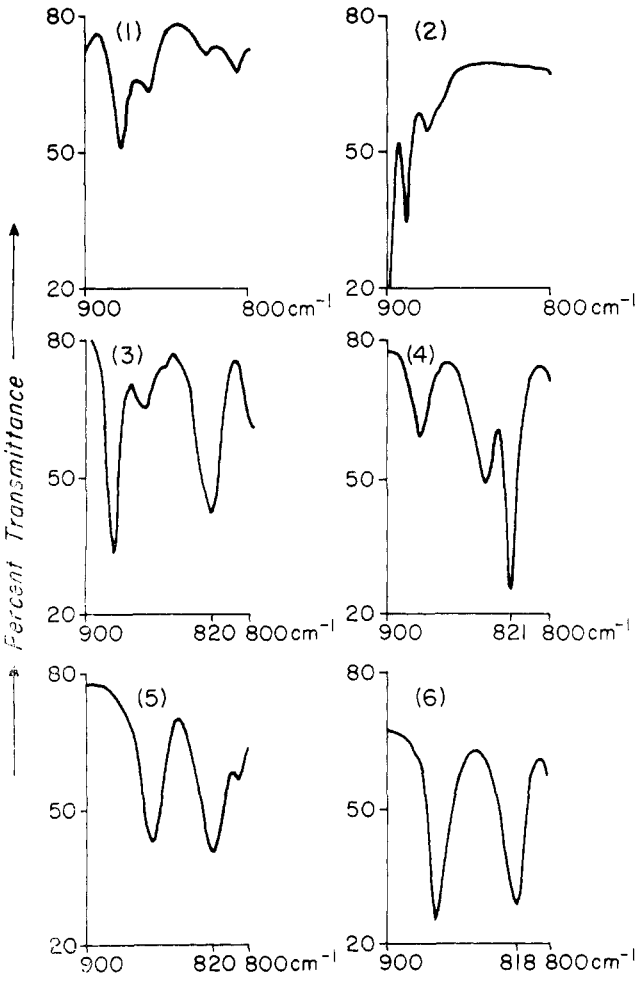
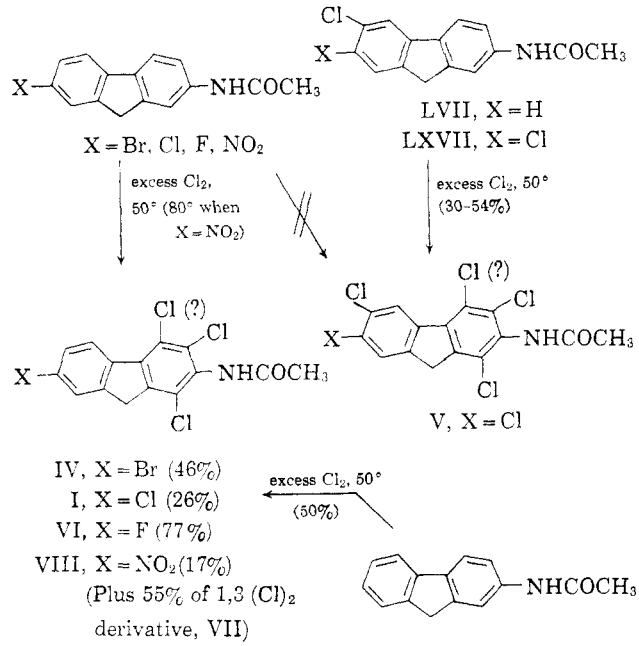



Fig. 1.—Infrared absorption at 900–800 cm.$^{-1}$ (1.5–1.8 mg. per 300 mg. of potassium bromide on a Beckman IR-5) of (1) N-2-(1,3,4(?),6,7-pentachlorofluorenyl)acetamide (V); (2) 9-oxo-3,6,7-trichloro-2-fluorenamine (XXXVIII); (3) N-2-(1,3,4(?),7-tetrachlorofluorenyl)acetamide (I); (4) N-2-(7-nitro-1,3,4(?)-trichlorofluorenyl)acetamide (VIII); (5) N-2-(7-fluoro-1,3,4(?)-trichlorofluorenyl)acetamide (VI); (6) N-2-(7-bromo-1,3,4(?)-trichlorofluorenyl)acetamide (IV).

rination of N-2-fluorenylacetamide or N-2-(9-oxofluorenyl)acetamide with molecular chlorine gave the 3-chloro compounds.[9] N-2-Fluorenylacetamide in glacial acetic acid (25°), containing a small amount of ferric chloride, with three molar equivalents of chlorine gave us N-2-(3,7-dichlorofluorenyl)acetamide (II). This had also been obtained by chlorination of either N-2-(3-chlorofluorenyl)acetamide (LVI) or N-2-(7-chlorofluorenyl) acetamide[10] with two molar equivalents of chlorine. Likewise, monochlorination of N-2-(7-chloro-9-oxofluorenyl)acetamide (LIX) or dichlorination of N-2-(9-oxofluorenyl)acetamide led to the formation of N-2-(3,7-dichloro-9-oxofluorenyl)-acetamide (X) identical (mixture melting point and infrared spectra) with the oxidation product of II.

Halogenation of 7-substituted N-2-fluorenylacetamide or 2-fluorenamine gave 1,3-disubstituted or 1,3,4(?)-trisubstituted compounds.[3] Bromination of 7-nitro-2-fluorenamine gave the 1,3-dibromo derivative (XVII), and of 7-bromo-2-fluorenamine gave 1,3,7-tribromo-2-fluorenamine (XVIII). In the chlorination of these 7-substituted N-2-fluorenylacetamides, trichloro (1,3,4?)[3] derivatives were obtained as summarized in the structures. The deactivating effect of the 7-nitro group lowered the yield of the trichloro compound and, as a consequence, a substantial amount of the 1,3-dichloro derivative was obtained.




As shown in the structural diagrams, attempts to obtain a pentachlorinated N-2-fluorenylacetamide by chlorination of this amide or of N-2-(7-chlorofluorenyl)-acetamide failed. However, we were able to obtain N-2-(1,3,4(?),6,7-pentachlorofluorenyl)acetamide (V) from both N-2-(6-chlorofluorenyl)acetamide (LVII) and N-2-(6,7-dichlorofluorenyl)acetamide (LXVIII).

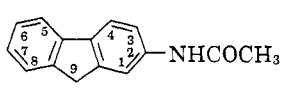
The infrared spectra of I, IV, VI, and VIII show strong absorption at 818–821 cm.$^{-1}$ which is absent in the spectra of the pentachloro-2-acetamidofluorene (V) and 9-oxo-3,6,7-trichloro-2-fluorenamine (XXXVIII) (Fig. 1). The presence of an absorption band in this region arises from the C–H out-of-plane bending vibration of the two adjacent hydrogen atoms[11] in positions 5 and 6 in the fluorene nucleus. From this evidence and the fact that unless a 6-chloro was already in position, none of these chlorinations yielded a 6-chloro polychlorinated derivative (which could have no absorption at 820 cm.$^{-1}$), we infer that in polychlorination of N-2-fluorenylacetamide or its 7-substituted derivatives, the third entering chlorine atom is in the 4- position[3] in compounds I, IV, VI, and VIII. For several reasons position 8, the only other one available, would seem highly unlikely.

N-2-(6-Chlorofluorenyl)acetamide (LVII), a key intermediate in elucidation of the structures of I, IV, VI, and VIII, was synthesized starting with N-2-(3-chloro-9-oxofluorenyl)acetamide (IX) which was prepared in high yields by method C (Experimental). Hydrolysis of this amide followed by trifluoroacetylation gave N-2-(3-chloro-9-oxofluorenyl)trifluoroacetamide (XLIII). Nitration of IX and XLIII gave, respectively, N-2-(3-chloro-7-nitro-9-oxofluorenyl)acetamide (XV) and N-2-(3-chloro-7-nitro-9-oxofluorenyl)-trifluoroacetamide (XLIV) in good yield (method D).

(9) F. Bell and J. A. Gibson, *J. Chem. Soc.*, 3560 (1955).
(10) S. Schulman, *J. Org. Chem.*, **14**, 382 (1949).
(11) (a) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd. Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 78; (b) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Holden-Day, Inc., San Francisco, Calif., 1962, p. 26.

TABLE I

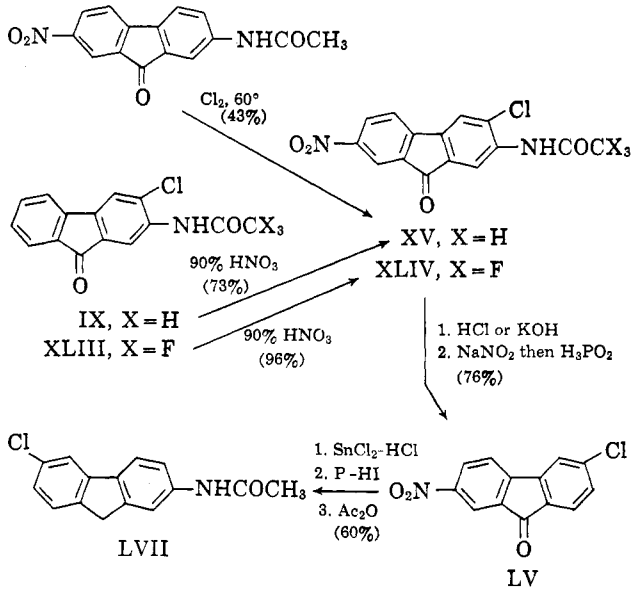
CHLORINATION OF N-2-FLUORENYLACETAMIDES



| | Molar equiv. of chlorine | Reaction temp., °C. | Reaction time, hr. | Method | Product: Position of Cl | Product: No. | Yield, % |
|---|---|---|---|---|---|---|---|
| Unsubstituted | [a] | 50–60 | 14 | A | 1,3,4(?),7 | I | 50 |
| | 3 | 25 | 1 | B | 3,7 | II | 31 |
| 7-AcNH | [a] | 50–55 | 5 | A | 1,3,6,8 | III | 93 |
| 7-Br | [a] | 50–55 | 3.5 | A | 1,3,4(?) | IV | 46 |
| 3-Cl | 2 | 25 | 6 | B | 3,7 | II | 37 |
| 6-Cl | [a] | 50–60 | 3 | A | 1,3,4(?),6,7 | V | 54 |
| 7-Cl | [a] | 50–60 | 2 | A | 1,3,4(?),7 | I | 26 |
| | 2 | 25 | 6 | B | 3,7 | II | 58 |
| 6,7-Di-Cl | [a] | 60–65 | 3.5 | A | 1,3,4(?),6,7 | V | 30 |
| 7-F | [a] | 50 | 3 | A | 1,3,4(?) | VI | 77 |
| 7-$NO_2$ | [a] | 65 | 5 | A | 1,3 | VII | 74 |
| | [a] | 80–85 | 6 | A | 1,3,4(?) | VIII | 17 |
| 9-Oxo | 1.1 | 40–45 | 5 | C | 3 | IX | 88 |
| | [a] | 80 | 9 | A | 3,7 | X | 58 |
| 6-Cl-9-oxo | 1.1 | 50 | 2 | C | 3,6 | XI | 93 |
| 7-Cl-9-oxo | 1.3 | 50 | 2 | C | 3,7 | X | 83 |
| 6,7-($Cl_2$)-9-oxo | 2 | 90–95 | 0.5 | C | 3,6,7 | XII | 100 |
| 7-F-9-oxo | 1.2 | 50–55 | 1.2 | C | 3 | XIII | 66 |
| 3-$NO_2$-9-oxo | 1 | 90–95 | 5.5 | C | 7 | XIV | <1 |
| 7-$NO_2$-9-oxo | 1.4 | 60 | 4.5 | C | 3 | XV | 43 |

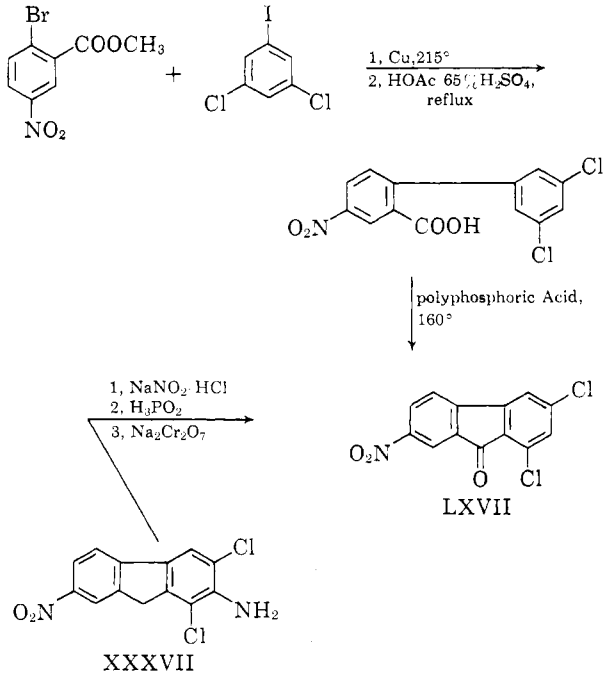
[a] In large excess.

The structure of XV was established by monochlorination of N-2-(7-nitro-9-oxofluorenyl)acetamide (method C) which gave the same chloro compound. Hydrolysis of XV or XLIV gave the amine XXXVI. Deamination to 3-chloro-7-nitro-9-oxofluorene (LV) (method I) followed by reduction gave 6-chloro-9-oxo-2-fluorenamine (XXXIV) which was reduced to 6-chloro-2-fluorenamine (XXXIII).




Acid hydrolysis of N-2-(1,3-dichloro-7-nitrofluorenyl)acetamide (VII) to XXXVII followed by deamination and dichromate oxidation gave 1,3-dichloro-7-nitro-9-oxofluorene (LXVII). The latter structure was proved unambiguously by an Ullmann condensation between 3,5-dichloroiodobenzene and methyl 2-bromo-5-nitrobenzoate, followed by hydrolysis of the ester and cyclization in polyphosphoric acid.

Hydrazine hydrate–Raney nickel reduction[12] of VII, to N-2-(7-amino-1,3-dichlorofluorenyl)acetamide (LXII), was followed by deamination to N-2-(1,3-dichlorofluorenyl)acetamide (LX) which could not be obtained by direct chlorination. Dichromate oxidation of LX gave a high yield of N-2-(1,3-dichloro-9-oxofluorenyl)acetamide (LXI).




N-2-(1,3-Dichloro-7-fluorofluorenyl)acetamide (LXIII) was prepared by diazotization of LXII in 48% fluoroboric acid followed by decomposition of the diazonium fluoroborate in boiling xylene. N-2-(1,3,7-Trichlorofluorenyl)acetamide (LXIX) was prepared from LXII through a Sandmeyer reaction.

Chlorination of N-2-(9-oxofluorenyl)acetamide and its derivatives with equimolar (or slightly excess) chlorine gave the 3-chloro compounds exclusively (Table I). Likewise, monochlorination of N-2-(6-chloro-9-oxofluorenyl)acetamide (LVIII) led to N-2-

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

TABLE II

HALOGENOFLUORENES AND DERIVATIVES

| No. | Name | M.p., °C.[a] | Yield, % | Method | Empirical formula | %C[b] Calcd. | %C Found | %H Calcd. | %H Found | %N Calcd. | %N Found | %Cl Calcd. | %Cl Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | N-2-(1,3,4(?),7-Tetrachlorofluorenyl)acetamide | 282–282.5 | [c] | [c] | $C_{15}H_9Cl_4NO$ | 49.90 | 50.04 | 2.51 | 2.51 | 3.88 | 3.91 | 39.28 | 39.25 |
| II | N-2-(3,7-Dichlorofluorenyl)acetamide | 265–266 | [c] | [c] | $C_{15}H_{11}Cl_2NO$ | 61.66 | 62.06 | 3.80 | 3.79 | 4.79 | 4.79 | 24.27 | 24.47 |
| III | N-2-(7-Acetamido-1,3,6,8-tetrachlorofluorenyl)-acetamide | 332–333 | [c] | [c] | $C_{17}H_{12}Cl_4N_2O_2$ | 48.83 | 48.54 | 2.89 | 2.79 | 6.70 | 6.38 | 33.92 | 33.98 |
| IV | N-2-(7-Bromo-1,3,4(?)-trichlorofluorenyl)acetamide | 281–282 | [c] | [c] | $C_{15}H_9BrCl_3NO$ | 44.43 | 44.45 | 2.24 | 2.12 | | | 26.23<br>Br<br>19.77 | 26.58<br>Br<br>19.73 |
| V | N-2-(1,3,4(?),6,7-Pentachlorofluorenyl)acetamide | 306–307 | [c] | [c] | $C_{15}H_8Cl_5NO$ | 45.55 | 45.55 | 2.04 | 2.06 | 3.54 | 3.48 | 44.82 | 44.61 |
| VI | N-2-(7-Fluoro-1,3,4(?)-trichlorofluorenyl)acetamide | 276–277 | [c] | [c] | $C_{15}H_9Cl_3FNO$ | 52.28 | 52.49 | 2.63 | 2.82 | 4.07 | 3.85 | 30.87 | 30.89 |
| VII | N-2-(1,3-Dichloro-7-nitrofluorenyl)acetamide | 265–266 | | [c] | $C_{15}H_{10}Cl_2N_2O_3$ | 53.43 | 53.25 | 2.99 | 3.00 | 8.31 | 8.31 | 21.03 | 21.35 |
| VIII | N-2-(7-Nitro-1,3,4(?)-trichlorofluorenyl)acetamide | 291–292 | [c] | [c] | $C_{15}H_9Cl_3N_2O_3$ | 48.48 | 48.65 | 2.44 | 2.52 | 7.54 | 7.46 | 28.62 | 28.42 |
| IX | N-2-(3-Chloro-9-oxofluorenyl)acetamide | 263.5–264.5[d] | [c] | [c] | $C_{15}H_{10}ClNO_2$ | 66.31 | 66.33 | 3.71 | 3.84 | 5.16 | 5.40 | 13.05 | 12.99 |
| X | N-2-(3,7-Dichloro-9-oxofluorenyl)acetamide | 291–292 | [c] | [c] | $C_{15}H_9Cl_2NO_2$ | 58.85 | 58.67 | 2.96 | 2.90 | 4.58 | 4.59 | 23.16 | 23.09 |
| XI | N-2-(3,6-Dichloro-9-oxofluorenyl)acetamide | 323–324 | [c] | [c] | $C_{15}H_9Cl_2NO_2$ | | | | | 4.58 | 4.55 | 23.16 | 22.85 |
| XII | N-2-(9-Oxo-3,6,7-trichlorofluorenyl)acetamide | 325–326 | [c] | [c] | $C_{15}H_8Cl_3NO_2$ | 52.90 | 52.77 | 2.37 | 2.34 | 4.11 | 4.11 | 31.23 | 31.13 |
| XIII | N-2-(3-Chloro-7-fluoro-9-oxofluorenyl)acetamide | 290.5–291.5 | [c] | [c] | $C_{15}H_9ClFNO_2$ | 62.19 | 62.38 | 3.13 | 3.55 | 4.84 | 4.59 | 12.24 | 12.53 |
| XIV | N-2-(7-Chloro-3-nitro-9-oxofluorenyl)acetamide | 310–311 | 95 (<1[e]) | D | $C_{15}H_9ClN_2O_4$ | 56.89 | 56.85 | 2.87 | 2.94 | 8.85 | 8.65 | 11.20 | 11.36 |
| XV | N-2-(3-Chloro-7-nitro-9-oxofluorenyl)acetamide | 319–320 | 73 (43[e]) | D | $C_{15}H_9ClN_2O_4$ | 56.89 | 57.05 | 2.86 | 2.91 | | | | |
| XVI | N-2-(3-Bromo-7-fluorofluorenyl)acetamide | 234.5–235 | 87 | E | $C_{15}H_{11}BrFNO$ | 56.27 | 56.39 | 3.46 | 3.43 | 4.38 | 4.39 | Br<br>24.96 | Br<br>24.80 |
| XVII | 1,3-Dibromo-7-nitro-2-fluorenamine | 251–251.5 | 87 | E | $C_{13}H_8Br_2N_2O_2$ | 40.66 | 40.67 | 2.10 | 2.03 | 7.30 | 7.24 | Br<br>41.62 | Br<br>41.78 |
| XVIII | 1,3,7-Tribromo-2-fluorenamine | 208–209[e] | 83 | E | $C_{13}H_8Br_3N$ | 37.36 | 37.61 | 1.93 | 2.05 | 3.35 | 3.32 | Br<br>57.36 | Br<br>57.30 |
| XIX | 9-Bromo-2,3,7-trichlorofluorene | 190.5–191 | 59 | F | $C_{13}H_6BrCl_3$ | 44.81 | 44.71 | 1.74 | 1.63 | | | 30.53<br>Br<br>22.93 | 30.70<br>Br<br>22.72 |
| XX | 2,3,7-Trichlorofluoren-9-ol | 175–175.5 | 100 | [f] | $C_{13}H_7Cl_3O$ | 54.68 | 54.70 | 2.47 | 2.42 | | | | |
| XXI | 9-Oxo-2,3,7-trichlorofluorene | 183.5–184[g] | 83 (68[g]) | [h] | $C_{13}H_5Cl_3O$ | 55.07 | 55.00 | 1.78 | 1.89 | | | 37.51 | 37.42 |
| XXII | 2-(2-Chlorobenzylideneamino)-7-chlorofluorene | 196.5–197.5 | 98 | G | $C_{20}H_{13}Cl_2N$ | | | | | 4.14 | 4.10 | | |
| XXIII | 2-(2-Chlorobenzylideneamino)-7-chloro-9-oxofluorene | 216–217 | 58 | G | $C_{20}H_{11}Cl_2NO$ | 68.20 | 68.41 | 3.15 | 3.10 | 3.98 | 3.78 | | |
| XXIV | 2-(2-Chlorobenzylideneamino)-3-chloro-9-oxofluorene | 224–225 | 60 | G | $C_{20}H_{11}Cl_2NO$ | 68.20 | 68.10 | 3.15 | 3.17 | 3.98 | 3.81 | 20.13 | 19.98 |
| XXV | 2-(3,4-Dichlorobenzylideneamino)-3-chloro-9-oxofluorene | 254–255 | 90 | G | $C_{20}H_{10}Cl_3NO$ | 62.12 | 62.39 | 2.61 | 2.50 | 3.62 | 3.57 | | |
| XXVI | 3,9-Dibromo-2-fluorenamine hydrobromide | | 80 | [i] | $C_{13}H_9Br_2N\cdot HBr$ | 37.18 | 37.20 | 2.40 | 2.51 | 3.34 | 3.33 | Br<br>57.09 | Br<br>56.90 |
| XXVII | 2-Amino-3-bromo-7-fluorofluoren-9-ol | 214.5–215 | 93 | [f] | $C_{13}H_9BrFNO$ | 53.09 | 53.06 | 3.08 | 3.22 | 4.76 | 4.98 | | |
| XXVIII | 3-Bromo-7-fluoro-9-oxo-2-fluorenamine | 217–218 | 92 | [i] | $C_{13}H_7BrFNO$ | | | | | 4.80 | 4.57 | | |
| XXIX | 3-Bromo-7-nitro-2-fluorenamine | 255.5–256.5 | 3 | [j] | $C_{13}H_9BrN_2O_2$ | | | | | 9.18 | 9.19 | Br<br>26.19 | Br<br>26.08 |
| XXX | 3-Bromo-7-nitro-9-oxo-2-fluorenamine | 286.5–287.5 | 59 | [k] | $C_{13}H_7BrN_2O_3$ | 48.93 | 48.89 | 2.21 | 2.26 | 8.78 | 8.65 | | |
| XXXI | 3-Bromo-6,7-dichloro-9-oxo-2-fluorenamine | 326–327 | 50 | [j] | $C_{13}H_6BrCl_2NO$ | | | | | 4.08 | 4.02 | Br<br>23.30 | Br<br>22.92 |
| XXXII | 3-Chloro-9-oxo-2-fluorenamine | 204–204.5[l] | 81 | [m] | $C_{13}H_8ClNO$ | 67.99 | 67.97 | 3.51 | 3.62 | 6.10 | 6.05 | | |
| XXXIII | 6-Chloro-2-fluorenamine | 97–98 | 65 | [n] | $C_{13}H_{10}ClN$ | 72.39 | 72.58 | 4.67 | 4.68 | 6.50 | 6.75 | 15.44 | 15.65 |
| XXXIV | 6-Chloro-9-oxo-2-fluorenamine | 221.5–222.5 | 78 | [o] | $C_{13}H_8ClNO$ | 67.99 | 67.78 | 3.51 | 3.38 | 6.10 | 6.30 | | |
| XXXV | 3-Chloro-9-oxo-2,7-fluorenediamine | 264–265 | 92 | [p] | $C_{13}H_9ClN_2O$ | | | | | 11.45 | 11.25 | 14.49 | 14.63 |
| XXXVI | 3-Chloro-7-nitro-9-oxo-2-fluorenamine | 305.5–306.5 | 89 | [k] | $C_{13}H_7ClN_2O_3$ | 56.85 | 57.00 | 2.57 | 2.65 | 10.20 | 10.06 | | |
| XXXVII | 1,3-Dichloro-7-nitro-2-fluorenamine | 233–234 | 87 | [m] | $C_{13}H_8Cl_2N_2O_2$ | | | | | 9.49 | 9.65 | | |

TABLE II (*Continued*)

| No. | Name | M.p., °C.[a] | Yield, % | Method | Empirical formula | % C[b] Calcd. | % C Found | % H Calcd. | % H Found | % N Calcd. | % N Found | % Cl Calcd. | % Cl Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XXXVIII | 9-Oxo-3,6,7-trichloro-2-fluorenamine | 339–340 | 43 | [m] | $C_{13}H_6Cl_3NO$ | | | | | 4.69 | 4.80 | 35.63 | 35.27 |
| XXXIX | N-2-(7-Nitrofluorenyl)dichloracetamide | 243–244 | 82 | [p] | $C_{15}H_{10}Cl_2N_2O_3$ | 53.43 | 53.71 | 2.90 | 2.88 | 8.31 | 8.42 | | |
| XL | N-2-(7-Bromofluorenyl)trifluoroacetamide | 232–233 | 95 | [q] | $C_{15}H_9BrF_3NO$ | 50.59 | 50.71 | 2.55 | 2.74 | 3.93 | 3.96 | | |
| XLI | N-2-(3-Bromo-9-oxofluorenyl)trifluoroacetamide | 251–252 | 99 | [q] | $C_{15}H_7BrF_3NO_2$ | 48.67 | 48.69 | 1.91 | 1.88 | 3.79 | 3.61 | | |
| XLII | N-2-(3-Bromo-7-nitro-9-oxofluorenyl)trifluoroacetamide | 252–253 | 75 | D | $C_{15}H_6BrF_3N_2O_4$ | 43.40 | 43.28 | 1.46 | 1.40 | 6.75 | 7.00 | | |
| XLIII | N-2-(3-Chloro-9-oxofluorenyl)trifluoroacetamide | 249–250 | 86 | [q] | $C_{15}H_7ClF_3NO_2$ | 55.32 | 55.44 | 2.17 | 2.18 | 4.30 | 4.32 | | |
| XLIV | N-2-(3-Chloro-7-nitro-9-oxofluorenyl)trifluoroacetamide | 250.5–251 | 70 | D | $C_{15}H_6ClF_3N_2O_4$ | 56.89 | 56.85 | 2.87 | 2.94 | 8.85 | 8.65 | 11.20 | 11.36 |
| XLV | 2-Bromo-9-oxo-1-fluorenamine | 179–179.5 | 35 | [n] | $C_{13}H_8BrNO$ | | | | | 5.11 | 5.01 | Br 29.15 | Br 29.22 |
| XLVI | 2,4-Dibromo-9-oxo-1-fluorenamine | 210–210.5 | 10–83 | [n] | $C_{13}H_7Br_2NO$ | 44.23 | 44.48 | 2.00 | 2.14 | 3.97 | 4.19 | Br 45.27 | Br 45.88 |
| XLVII | 2,7-Dichlorofluorene | 125–126[r] | 52 | [n] | $C_{13}H_8Cl_2$ | | | | | | | 30.16 | 29.89 30.15 |
| XLVIII | 6,7-Dichloro-2-fluorenamine | 186.5–187.5 | 70 | [n] | $C_{13}H_9Cl_2N$ | | | | | 5.60 | 5.30 | 28.35 | 28.22 |
| XLIX | 6,7-Dichloro-9-oxo-2-fluorenamine | 239–240 | 84 | [o] | $C_{13}H_7Cl_2NO$ | | | | | 5.30 | 5.17 | Br 26.85 | Br 26.97 |
| L | N-2-(6,7-Dichloro-9-oxofluorenyl)acetamide | 327–328 | 81 | [s] | $C_{15}H_9Cl_2NO_2$ | 58.85 | 59.15 | 2.94 | 3.30 | | | Br 23.16 | Br 23.24 |
| LI | 2,3-Dichloro-7-nitro-9-oxofluorene | 220–221 | 53 | H | $C_{13}H_5Cl_2NO_3$ | 53.09 | 53.47 | 1.71 | 1.91 | 4.76 | 4.96 | 24.11 | 23.84 |
| LII | 3-Amino-2,7-dichlorofluoren-9-ol | 206–207 | 96 | [f] | $C_{13}H_9Cl_2NO$ | | | | | 5.27 | 5.45 | | |
| LIII | 2,7-Dichloro-9-oxo-3-fluorenamine | 265–266[t] | 78 | [o] | $C_{13}H_7Cl_2NO$ | 59.12 | 59.13 | 2.67 | 2.66 | 5.30 | 5.25 | 26.85 | 26.73 |
| LIV | 9-Bromo-2-fluoro-7-nitrofluorene | 172.5–173.5 | 62 | F | $C_{13}H_7BrFNO_2$ | 50.68 | 51.06 | 2.29 | 2.33 | 4.55 | 4.48 | Br 25.94 | Br 25.90 |
| LV | 3-Chloro-7-nitro-9-oxofluorene | 288–289 | 80 | I | $C_{13}H_6ClNO_3$ | 60.14 | 60.23 | 2.33 | 2.47 | 5.40 | 5.41 | 13.66 | 13.44 |
| LVI | N-2-(3-Chlorofluorenyl)-acetamide | 211–212[u] | 55 | [s] | $C_{15}H_{12}ClNO$ | 69.91 | 69.78 | 4.69 | 4.74 | 5.44 | 5.48 | 13.76 | 13.73 |
| LVII | N-2-(6-Chlorofluorenyl)-acetamide | 219–220 | 85 | [s] | $C_{15}H_{12}ClNO$ | 69.91 | 69.84 | 4.69 | 4.66 | 5.44 | 5.30 | 13.76 | 13.80 |
| LVIII | N-2-(6-Chloro-9-oxofluorenyl)acetamide | 301.5–302.5 | 75 | [s] | $C_{15}H_{10}ClNO_2$ | 66.31 | 66.02 | 3.71 | 3.73 | 5.16 | 5.22 | | |
| LIX | N-2-(7-Chloro-9-oxofluorenyl)acetamide | 276.5–277 | 97 | [s] | $C_{15}H_{10}ClNO_2$ | 66.31 | 66.13 | 3.71 | 3.49 | 5.16 | 5.20 | | |
| LX | N-2-(1,3-Dichlorofluorenyl)acetamide | 238.5–239.5 | 33 | [v] | $C_{15}H_{11}Cl_2NO$ | 61.66 | 61.57 | 3.80 | 3.95 | 4.79 | 4.76 | 24.27 | 24.31 |
| LXI | N-2-(1,3-Dichloro-9-oxofluorenyl)acetamide | 261.5–262 | 48 | [h] | $C_{15}H_9Cl_2NO_2$ | | | | | 4.58 | 4.40 | | |
| LXII | N-2-(7-Amino-1,3-dichlorofluorenyl)acetamide | 236–237 | 77 | [w] | $C_{15}H_{12}Cl_2N_2O$ | 58.65 | 58.54 | 3.94 | 3.73 | 9.12 | 9.09 | | |
| LXIII | N-2-(1,3-Dichloro-7-fluorofluorenyl)acetamide | 268–269 | 40 | [n] | $C_{15}H_{10}Cl_2FNO^x$ | | | | | 4.52 | 4.40 | 22.86 | 22.85 |
| LXIV | N-2-(9-Oxo-1,3,4(?),7-tetrachlorofluorenyl)-acetamide | 278–279 | 73 | [h] | $C_{15}H_7Cl_4NO_2$ | 48.04 | 48.08 | 1.88 | 2.09 | 3.74 | 3.67 | 37.82 | 37.57 |
| LXV | 2-(3′,4′-Dichlorophenyl)-3-chloro-9-oxofluorene | 221.5–222.5 | 17 | [n] | $C_{19}H_9Cl_3O$ | 63.45 | 63.99 | 2.52 | 2.45 | | | 29.58 | 29.84 |
| LXVI | 1,3-Dichloro-7-nitrofluorene | 192–193 | 30 | [y] | $C_{13}H_7Cl_2NO_2$ | 55.74 | 55.93 | 2.52 | 2.80 | 5.00 | 4.82 | 25.32 | 25.20 |
| LXVII | 1,3-Dichloro-7-nitro-9-oxofluorene | 286–287 | 23 (32[h]) | [n] [h] | $C_{13}H_5Cl_2NO_3$ | 53.09 | 53.16 | 1.71 | 1.40 | 4.76 | 4.64 | 24.11 | 23.87 |
| LXVIII | N-2-(6,7-Dichlorofluorenyl)acetamide | 227.5–228.5 | 86 | [s] | $C_{15}H_{11}Cl_2NO$ | 61.66 | 61.96 | 3.80 | 3.99 | 4.79 | 4.72 | 24.27 | 24.28 |
| LXIX | N-2-(1,3,7-Trichlorofluorenyl)acetamide | 242.5–243.5 | 45 | H | $C_{15}H_{10}Cl_3NO$ | 55.16 | 55.06 | 3.09 | 3.30 | 4.29 | 4.17 | 32.57 | 32.68 |
| LXX | 3,6-Dichloro-9-oxo-2-fluorenamine | 286.5–287 | 35 | [m] | $C_{13}H_7Cl_2NO$ | | | | | 5.30 | 5.21 | | |
| LXXI | 3,6-Dichloro-9-oxofluorene | 300.5–301.5[z] | 74 | I | $C_{13}H_6Cl_2O$ | 62.68 | 62.85 | 2.43 | 2.58 | | | | |
| LXXII | N-2-(3-Bromo-7-fluoro-9-oxofluorenyl)acetamide | 291–292 | 76[h] (55[j,s]) | [h] [j,s] | $C_{15}H_9BrFNO_2$ | 53.92 | 54.00 | 2.72 | 2.90 | 4.19 | 4.06 | | |
| LXXIII | 2,3,7-Trichlorofluorene | 127.5–128 | 33 | [n] | $C_{13}H_7Cl_3$ | 57.92 | 58.04 | 2.62 | 2.80 | | | 39.46 | 39.39 |

[a] All melting points below 250° were taken on a Fisher–Johns block and are corrected to standards. The melting points above 250° were taken with a Hoover capillary melting point apparatus and are uncorrected. [b] A. Bernhardt, Mülheim (Ruhr), and Schwarzkopf Microanalytical Lab., Woodside, N. Y. [c] See Table I. [d] Reported m.p. 260°.[9] [e] Reported m.p. 205°.[5e] [f] From sodium borohydride–methanol reduction of the corresponding fluorenone. See H. L. Pan and T. L. Fletcher, *J. Org. Chem.*, **23**, 799 (1958). [g] Reported m.p. 265–266°.[8] This compound was also obtained in 68% yield from 3-amino-2,7-dichloro-9-oxofluorene (see method H). [h] From sodium dichromate–acetic acid oxidation of the corresponding fluorene. [i] From the reaction of 48% hydrobromic acid with the corresponding fluoren-9-ol. [j] From the reaction of 48% hydrobromic acid in dimethyl sulfoxide with the amine.[14] [k] From hydrolysis of the

TABLE II (*Continued*)

N-2-fluorenyltrifluoroacetamide with potassium hydroxide in ethanol. See M. J. Namkung and T. L. Fletcher, *J. Org. Chem.*, **25**, 740 (1960). [l] Reported m.p. 189°.[9] [m] From the hydrolysis of the N-2-fluorenylacetamide with concentrated hydrochloric acid in ethanol. [n] See Experimental. [o] From the reduction of the corresponding nitrofluorene with stannous chloride–hydrochloric acid. [p] From the reaction of dichloroacetyl chloride with the amine in warm *p*-dioxane. [q] From the reaction of trifluoroacetic anhydride with the amine in benzene or dichloromethane. [r] Reported m.p. 125–126°.[6] [s] From the amine with acetic anhydride in acetic acid. [t] Reported m.p. 208–209°.[7] [u] Reported m.p. 204°.[9] [v] From deamination of LXII (see method I). [w] From the reduction of the nitrofluorene with 85% hydrazine hydrate–Raney nickel in boiling ethanol.[12] [x] Calcd.: F, 6.13. Found: F, 5.87. [y] From deamination of XXXVII (see method I). [z] Reported m.p. 301°.[13]

TABLE III

ANTITUMOR ACTIVITY OF CERTAIN HALOGENOFLUORENES[a,b]

| Compound No. | Test system[c] | Daily dose, mg./kg. | Survivors | Antitumor activity: Animal wt. difference (T−C), g. | Antitumor activity: Tumor wt., mg. (T/C) | Antitumor activity: Per cent tumor wt. decrease | Specificity test[d]: Confidence, % | Specificity test[d]: Index |
|---|---|---|---|---|---|---|---|---|
| I | Sarcoma 180 | 500 | 6/6 | 4.4 | 594/783 | 25[e] | | |
| | Adenocarcinoma 755 | 450 | 9/10 | −3.0 | 300/1545 | 81 | | |
| | | 225 | 10/10 | −1.6 | 495/1545 | 68 | | |
| | | 110 | 10/10 | −2.2 | 1305/2853 | 55 | | |
| | | 55 | 8/10 | −2.9 | 1639/2853 | 43 | | |
| | | 25 | 10/10 | −2.1 | 1585/2853 | 45 | | |
| | | 12.5 | 10/10 | −1.3 | 2701/2853 | 6 | | |
| | | | | | | | 99.7 | 3.0 |
| VI | Sarcoma 180 | 750 | 4/6 | −1.2 | 275/1252 | 79 | | |
| | | 500 | 5/6 | −1.0 | 226/1252 | 82 | | |
| | | 333 | 6/6 | −0.7 | 354/1252 | 72 | | |
| | | 222 | 6/6 | .3 | 429/1252 | 66 | | |
| | | 125 | 6/6 | −2.0 | 423/522 | 19 | | |
| | | 62.5 | 6/6 | −1.3 | 410/522 | 22 | | |
| | Adenocarcinoma 755 | 450 | 10/10 | −4.2 | 246/1291 | 81[f] | | |
| | | 45 | 7/10 | −5.7 | 527/1974 | 74[g] | | |
| VII | Sarcoma 180 | 750 | 5/6 | −5.7 | 260/1119 | 77 | | |
| | | 500 | 6/6 | −4.3 | 187/1119 | 84 | | |
| | | 333 | 5/6 | −3.9 | 505/1119 | 55 | | |
| | | 222 | 5/6 | −1.0 | 675/1119 | 40 | | |
| | | | | | | | 95.0 | 2.0 |
| | Adenocarcinoma 755 | 400 | 9/10 | −3.7 | 186/904 | 80 | | |
| | | 200 | 10/10 | −3.1 | 244/904 | 74 | | |
| | | 100 | 9/10 | −1.8 | 277/904 | 70 | | |
| | | 50 | 10/10 | −3.9 | 321/904 | 65 | | |
| | | 25 | 10/10 | −2.6 | 345/1394 | 76 | | |
| | | 12.5 | 10/10 | −1.3 | 320/1394 | 78 | | |
| | | 6.25 | 9/10 | −0.2 | 833/1394 | 41 | | |
| | | | | | | | 99.7 | 2.2 |
| XVI | Sarcoma 180 | 500 | 5/6 | −5.8 | 330/1465 | 78 | | |
| | | 333 | 6/6 | −5.1 | 655/1465 | 56 | | |
| | | 222 | 6/6 | −3.0 | 833/1465 | 44 | | |
| XVII | Sarcoma 180 | 500 | 4/6 | −0.2 | 268/1252 | 79 | | |
| | | 333 | 5/6 | −0.8 | 265/1252 | 79 | | |
| | | 222 | 6/6 | −0.4 | 341/1252 | 73 | | |
| | | 148 | 6/6 | −0.3 | 1216/1262 | 4 | | |
| | | 74 | 6/6 | −0.6 | 983/1262 | 23 | | |
| | | | | | | | 95.0 | 3.5 |
| | Adenocarcinoma 755 | 900 | 10/10 | −6.3 | 298/1968 | 85 | | |
| | | 450 | 10/10 | −5.0 | 126/1968 | 94 | | |
| | | 225 | 10/10 | −5.9 | 344/1968 | 83 | | |
| | | 110 | 10/10 | −4.8 | 346/1968 | 83 | | |
| | | 55 | 10/10 | −1.6 | 430/1255 | 66 | | |
| | | 25 | 10/10 | −2.2 | 609/1255 | 52 | | |
| | | | | | | | 99.7 | 1.6 |
| XVIII | Sarcoma 180 | 125 | 5/6 | −0.2 | 645/1294 | 51[h] | | |
| | Adenocarcinoma 755 | 700 | 10/10 | −2.2 | 394/1136 | 66 | | |
| | | 350 | 10/10 | −1.6 | 188/1136 | 84 | | |
| | | 175 | 10/10 | −1.7 | 375/1136 | 67 | | |
| | | 87.5 | 10/10 | −1.0 | 450/1338 | 67 | | |
| | | 43.7 | 10/10 | −1.0 | 488/1338 | 63 | | |
| | | 21.8 | 10/10 | −0.1 | 934/1338 | 31 | | |
| | | | | | | | 99.7 | 3.9 |

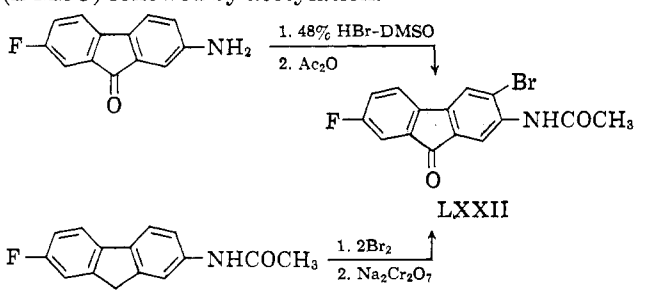
TABLE III (*Continued*)

| Compound No. | Test system[c] | Daily dose, mg./kg. | Survivors | Antitumor activity: Animal wt. difference ($T-C$), g. | Tumor wt., mg. ($T/C$) | Per cent tumor wt. decrease | Specificity test[d]: Confidence, % | Index |
|---|---|---|---|---|---|---|---|---|
| XIX | Sarcoma 180 | 750 | 4/6 | −7.0 | 350/1610 | 79 | | |
| | | 500 | 6/6 | −6.3 | 491/1610 | 70 | | |
| | | 333 | 6/6 | −5.2 | 437/1610 | 73 | | |
| | | 222 | 6/6 | −3.6 | 1075/1610 | 34 | | |
| XX | Sarcoma 180 | 500 | 5/6 | −7.1 | 115/1302 | 92[i] | | |
| | | 250 | 6/6 | −1.4 | 551/1273 | 57[g] | | |
| | Adenocarcinoma 755 | 200 | 10/10 | −4.7 | 64/648 | 70[j] | | |
| XXI | Sarcoma 180 | 750 | 4/6 | −5.1 | 443/1610 | 73 | | |
| | | 333 | 6/6 | −5.1 | 629/1610 | 61 | | |
| | | 222 | 5/6 | −3.4 | 785/1610 | 52 | | |
| XXII | Sarcoma 180 | 750 | 5/6 | −6.9 | 227/1098 | 80 | | |
| | | 500 | 5/6 | −6.6 | 248/1098 | 78 | | |
| | | 333 | 6/6 | −6.4 | 222/1098 | 80 | | |
| | | 222 | 5/6 | −5.0 | 513/1098 | 54 | | |
| | | 144 | 6/6 | −3.3 | 638/1511 | 58 | | |
| | | 96 | 5/6 | −2.8 | 780/1511 | 49 | | |
| | | | | | | | (Not significant) | |
| [k] | Lewis lung carcinoma | 400 | 5/6 | −5.1 | 510/1393 | 64[i] | | |
| | Sarcoma 180 | 560 | 5/6 | −6.7 | 361/1098 | 68 | | |
| | | 375 | 5/6 | −4.4 | 509/1098 | 54 | | |
| | | 250 | 5/6 | −5.6 | 396/1098 | 64 | | |
| | | 166 | 6/6 | −2.7 | 232/1098 | 79 | | |
| | | 110 | 6/6 | −2.4 | 535/1098 | 52 | | |
| | | | | | | | (Not significant) | |
| V | Sarcoma 180 | 250 | 6/7 | −3.0 | 511/1747 | 71[f] | | |

[a] The screening data in this Table were kindly supplied by the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda, Md. [b] Assays were performed according to specifications established by CCNSC as reported in *Cancer Chemotherapy Rept.*, **25**, 1 (1962). [c] Sarcoma 180 was tested in random bred Albino mice; Adenocarcinoma 755 and Lewis Lung Carcinoma were tested in $BDP_1$ mice. [d] This test, for solid tumor inhibition test systems, was developed by Southern Research Institute for determining whether the observed effects are caused by specific antitumor activity beyond that attributable to host inanition. A compound having confidence at the 99.7% level is considered truly specific. The specificity index is the ratio of the host weight change difference at a $T/C$ of 40% for the standard line [which relates the ratio of test to control tumor weights ($T/C$) to the host weight change difference ($T-C$)] to that of the test material (memorandum, Dr. Joseph Leiter, Chief, Drug Evaluation Branch, CCNSC). For details of this testing method see H. E. Skipper, W. S. Wilcox, F. M. Schabel, Jr., W. R. Laster, Jr., and L. Mattill, *Cancer Chemotherapy Rept.*, **29**, 1 (1963). Compounds being screened earlier than December, 1962, have no data on this test. [e] Activity not confirmed. [f] Activity confirmed but the compound has not yet been subjected to dose response tests. [g] Confirmation test [h] Nontoxic inactive. [i] Passed Stage 1 of sequential screen. [j] Passed Stage 3 of sequential screen. [k] N-2-(3-Bromo-9-hydroxyfluorenyl)acetamide. See footnote *f*, Table II.

(3,6-dichloro-9-oxofluorenyl)acetamide (XI) which, after hydrolysis and deamination, gave the known compound, 3,6-dichloro-9-oxofluorene.[13]

An attempt to prepare N-2-(1,3-dibromo-7-fluorofluorenyl)acetamide by reaction of N-2-(7-fluorofluorenyl)acetamide with two molar equivalents of bromine failed. Instead N-2-(3-bromo-7-fluorofluorenyl)acetamide (XVI) was formed, which was oxidized to the corresponding fluorenone LXXII. The latter was also prepared by brominating 7-fluoro-9-oxo-2-fluorenamine with 48% hydrobromic acid in dimethyl sulfoxide[14] (DMSO) followed by acetylation.




(13) E. H. Huntress and I. S. Cliff, *J. Am. Chem. Soc.*, **55**, 2559 (1933).

(14) T. L. Fletcher, M. J. Namkung, and H. L. Pan, *Chem. Ind.* (London), 660 (1957

2-Bromo-9-oxo-1-fluorenamine (XLV) and 2,4-dibromo-9-oxo-1-fluorenamine (XLVI) were obtained by brominating 9-oxo-1-fluorenamine in acetic acid.

## Experimental

Chlorination reactions were run in partial darkness by wrapping reaction vessels in aluminum foil.

**General Procedures. A.**—Chlorine was bubbled at a moderate rate (Matheson 620 BMV flowmeter with standard glass float) through a solution of N-2-fluorenylacetamide (or derivative) and anhydrous ferric chloride (~5% by wt. of the amide) in glacial acetic acid (0.1–0.3 l./0.01 mole of the amide) while the mixture was stirred and heated at the desired temperature. The reaction mixture was then set aside overnight, the product isolated, and recrystallized from acetic acid, ethanol, or toluene.

**B.**—N-2-Fluorenylacetamide (or derivative) and anhydrous ferric chloride (~10% by wt. of the amide) were dissolved in glacial acetic acid (same amount as in method A). To the stirred mixture chlorine (2–3 molar equivalents) in glacial acetic acid (0.1 l./0.1 mole of chlorine) was added in one portion. The reaction mixture was stirred for several hours, and the product filtered and recrystallized from ethanol.

**C.**—Chlorine (1–2 molar equivalents) in glacial acetic acid was added dropwise to a stirred mixture of N-2-(9-oxofluorenyl)-acetamide (or derivative), anhydrous ferric chloride (1–5% by wt. of the amide), and glacial acetic acid (0.1–1 l./0.01 mole of the amide) over a period of 0.5–5.5 hr. while the reaction mixture was maintained at the desired temperature. Stirring was continued

for a few hours and water was added. The product was filtered and recrystallized from a suitable solvent. Alternatively the corresponding amine was acetylated in the reaction medium prior to the chlorination.

**D.**—The N-fluorenylacetamide or N-fluorenyltrifluoroacetamide (0.1 mole) was added in small portions, during 5 min., to a stirred mixture of 90% nitric acid (120 ml.) and glacial acetic acid (120 ml.) held at 35–40°. To the suspension, concentrated sulfuric acid (30 ml.) was added at such a rate that the temperature of the reaction mixture did not rise above 55° (10 min.). This was then allowed to cool and was diluted with ice–water. The product was isolated and recrystallized from acetone or chloroform.

**E.**—The 7-substituted 2-fluorenamine or acetamide was dissolved in chlororoform or acetic acid (120 ml./0.01 mole of the amine or amide). To the stirred solution, bromine (2 molar equivalents) was added in small portions within 30 min. and stirring was continued for 20–40 hr. Then the product was filtered, treated with dilute ammonium hydroxide, and recrystallized from acetone, chloroform, toluene, or methanol.

**F.**—2,3,7-Trichlorofluorene (for XIX) or 2-fluoro-7-nitrofluorene (for LIV) was dissolved in carbon tetrachloride (1.5 l./0.1 mole) or benzene (0.5 l./0.1 mole). After adding 1 molar equivalent of *N*-bromosuccinimide, the solution was refluxed and illuminated with a G. E. purple-X 250-w. bulb for 1–2 hr., and filtered while hot. The product, from the filtrate, was recrystallized from benzene–ligroin (*d* 0.67–0.69) or ethanol.

**G.**—The chlorobenzaldehyde (1 equiv.) in absolute ethanol (25 ml./0.02 mole) was added in one portion to a stirred warm solution of the fluorenamine in absolute ethanol or glacial acetic acid (300–350 ml./0.02 mole). The reaction mixture was stirred at 25°, or at the boiling temperature (for 3-chloro-2-fluorenamine), for 0.5–1 hr. and cooled. After water dilution the azomethine was isolated and recrystallized from ethanol, acetone, or chloroform.

**H.**—3-Chloro-7-nitro-9-oxo-2-fluorenamine (for LI) or N-2-(7-amino-1,3-dichlorofluorenyl)acetamide (for LXIX) was diazotized in concd. HCl (300 ml./0.1 mole of the amine) at 0–5° with a solution of sodium nitrite (1.1 equiv.). The mixture was stirred at 0° for 0.5–1 hr. and a solution of cuprous chloride (1 equiv.) in cold concentrated hydrochloric acid was then added slowly. The reaction mixture was stirred continuously at 25° for 1–2 hr. then heated in a hot water bath for 10–30 min., and diluted. The product was filtered, washed, and recrystallized from ethanol or chromatographed through an alumina column with chloroform or benzene as eluent.

**I.**—A mixture of 3-chloro-7-nitro-9-oxo-2-fluorenamine (for LV) or 3,6-dichloro-9-oxo-2-fluorenamine (for LXXI) and 25% hydrochloric acid (0.1–0.3 l./0.01 mole of the amine) was heated to boiling, cooled to 5°, and diazotized with sodium nitrite (1.5 equiv.). Cold 50% hypophosphorous acid (100 ml./0.01 mole of amine) was then slowly added. The mixture was refrigerated overnight then warmed to 25°, diluted, and the product isolated, recrystallized from acetic acid, toluene, or benzene, or chromatographed through an alumina column with benzene as eluent.

**2,7-Dichlorofluorene (XLVII).**—Fluorene (26 g., 0.16 mole) was dissolved in glacial acetic acid (500 ml.) at ~40° with anhydrous ferric chloride (2–3 g.) and chlorine was bubbled in until a weight gain of 34.1 g. (0.48 mole) was observed. The mixture was stirred for 1 hr. and for an additional 2.5 hr. at 65–70°, then kept at 60° overnight. It was then heated to 90° and cooled. After water dilution the precipitate was dried and recrystallized from methanol giving shiny platelets.

**2,3,7-Trichlorofluorene (LXXIII). (a).**—Chlorine (71 g., 1 mole) in acetic acid (800 ml.) was added dropwise with stirring to fluorene (50 g., 0.3 mole) and anhydrous ferric chloride (4 g.) in the same solvent (1.5 l.) over a period of 5 hr. while the mixture was heated at 90–95°. After the addition was complete, stirring was continued at the same temperature for 2.5 hr. The solution was kept at 60° overnight. It was then boiled, and water was added to the point of cloudiness. The cooled mixture was filtered, and the product crystallized from methanol to give silky needles.

**(b).**—3-Amino-2,7-dichlorofluorene[7] was converted to the product by method H.

**2-Bromo-9-oxo-1-fluorenamine (XLV).**—Bromine (8 g., 0.05 mole) in glacial acetic acid (50 ml.) was added dropwise to a stirred solution of 9-oxo-1-fluorenamine (9.8 g., 0.05 mole) in the same solvent at 15° (40 min.). Stirring was continued for 20 min. and an excess of aqueous sodium acetate added. The orange-yellow precipitate was filtered, washed with water, and dried, giving 14.2 g. of a mixture. Recrystallization from acetone–methanol gave the dibromo compound as orange-yellow needles. The acetone–methanol filtrate, upon concentration, gave the product which was recrystallized from methanol and chromatographed in benzene through an alumina column (35%).

**2,4-Dibromo-9-oxo-1-fluorenamine (XLVI).**—The first crop from the crystallization of the crude mixture above was recrystallized twice from acetone giving golden yellow leaflets (10%). A much higher yield (83%) of the dibromo derivative was obtained using 2 molar equiv. of bromine, 22 hr. at 25°, after an initial short period at 50–70°.

**6-Chloro-2-fluorenamine (XXXIII).**—6-Chloro-9-oxo-2-fluorenamine (XXXIV) (5.7 g.) was reduced by refluxing 44 hr. in a mixture of red phosphorus (13 g.), 47% hydriodic acid (18 ml.), and glacial acetic acid (250 ml.). After removal of the solvent the amine was extracted with hot 5% hydriodic acid. Concentrated ammonium hydroxide released the free amine. Recrystallization from methanol–water, then from benzene–petroleum ether (b.p. 30–60°) gave snow white needles, 3.4 g.

**6,7-Dichloro-2-fluorenamine (XLVIII).**—2,3-Dichloro-7-nitro-9-oxofluorene (LI) (5 g.) was suspended in a mixture of 2,2′-oxydiethanol (300 ml.) and 85% hydrazine hydrate (30 ml.) which was gently refluxed for 26 hr. The condenser was then removed and heating was continued until the temperature of the light yellow solution reached 210°. After cooling and dilution of the mixture, the product was filtered, dried, and recrystallized from benzene–ligroin (*d* 0.67–0.69) and from methanol giving silky needles.

**N-2-(1,3-Dichloro-7-fluorofluorenyl)acetamide (LXIII).**—N-2-(7-Amino-1,3-dichlorofluorenyl)acetamide (LXII) (11.2 g., 0.037 mole) was diazotized at 0° with sodium nitrite (2.8 g., 0.04 mole) in 48% fluoroboric acid (200 ml.). The diazonium fluoroborate (dec. ~130°) was washed, dried, and decomposed in boiling xylene (200 ml.) which was boiled to near dryness. The product was recrystallized from acetone and from ethanol giving short needles.

**2-(3,4-Dichlorophenyl)-3-chloro-9-oxofluorene (LXV).**—3-Chloro-9-oxo-2-fluorenediazonium fluoroborate (4 g.), prepared by diazotization of 3-chloro-9-oxo-2-fluorenamine (XXXII) in 48% fluoroboric acid, was suspended in *o*-dichlorobenzene (100 ml.). The suspension was refluxed for 1 hr. and cooled. The reaction solution was passed through an alumina column. A yellow band was eluted with benzene and the solvent evaporated giving crystals (3 g.) which were recrystallized from benzene–ligroin (*d* 0.67–0.69). The product was twice more chromatographed and recrystallized again to give the pure, and unexpected, product as bright yellow needles.

**1,3-Dichloro-7-nitro-9-oxofluorene (LXVII). (a).**—3,5-Dichloroiodobenzene (14.2 g., 0.052 mole), prepared by the Sandmeyer reaction on 3,5-dichloroaniline (Gallard-Schlesinger Chemical Mfg. Corp., Garden City, N. Y.), methyl 2-bromo-5-nitrobenzoate[15] (26 g., 0.1 mole), and Copper Bronze powder (British Drug Houses, Ltd.) (30 g.) were mixed and heated with rapid stirring at 190–210° (bath) for 30 min. The temperature was gradually raised to 220° while more Copper Bronze (30 g.) was added in small portions over a period of 1 hr. and stirring was continued at this temperature for 0.5 hr. After cooling, extraction with acetone, and filtration, the solid from the acetone was refluxed for 8 hr. in a mixture of acetic acid (400 ml.) and 65% sulfuric acid (300 ml.). The mixture was then diluted with ice–water and the precipitate filtered, treated with hot 15% sodium carbonate (200 ml.), and the carbonate-soluble material was dried (8 g.) and mixed with polyphosphoric acid (80 g.) (Victor Chemical). This was heated with occasional stirring at 150–160° (oven) for 1.5 hr. and cooled. After dilution with ice–water the yellow precipitate was separated, treated with hot 15% sodium carbonate (200 ml.), and the carbonate-insoluble product was recrystallized from toluene giving shiny yellow needles.

**(b).**—1,3-Dichloro-7-nitrofluorene (LXVI) (prepared by deamination of XXXVII) (2.1 g.) was oxidized in boiling glacial acetic acid (75 ml.) with sodium dichromate (7 g.) (10 min.). Recrystallization from toluene followed by chromatography through alumina (benzene) gave the pure product; melting point, mixture melting point, and infrared spectra indicated that this material and the product obtained from procedure a were identical.

**Acknowledgment.**—The authors are indebted to Marylin E. Sanford for very substantial assistance in the preparation of some of the starting materials.

(15) F. Ullmann and J. Bielecki, *Ber.*, **34**, 2174 (1901).