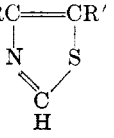
TABLE VII

4- AND 5-SUBSTITUTED THIAZOLES



No.	R	R′	M.P., ° Obtained	M.P., ° Reported	% Yield, Crude	Empirical Formula	% N Calcd.	% N Found	% S Calcd.	% S Found
XXV	CH_3	$COOC_2H_5$	98–99°/3 mm.[a]	140°/12 mm.[7]	51.4	$C_7H_9NO_2S$	8.18	8.16	18.73	18.62
XXVI	$COOC_2H_5$	H	52–54[b]	57[8]	44.6	$C_6H_7NO_2S$	8.91	8.92	—	—
XXVII	CH_3	COOH	255[c]	255[7]	82.9	$C_5H_5NO_2S$	9.78	9.41	22.40	22.73

[a] Boiling point. [b] Recrystallization from heptane. [c] Recrystallization from water.

dried over sodium sulfate. The ether was removed *in vacuo* at a maximum temperature of 80–90°.

To a stirred solution containing 32 g. (0.17 mole) of I, 200 ml. of ethyl alcohol, and 11.1 g. (0.17 mole) of 85% potassium hydroxide was added 27.2 g. (0.17 mole) of 3-bromocyclohexene. An exothermic reaction set in causing the temperature to rise from 25 to 48°. After stirring at 25–30° for 24 hr., 200 ml. of water and 300 ml. of ethyl ether were added. The ether solution was separated, washed with water until the wash water was neutral to litmus, and dried over sodium sulfate. The ether was removed *in vacuo* at a maximum temperature of 80–90°. The data are summarized in Table V.

2,3 - Bis(2 - benzothiazolylthio) - 1,4 - naphthoquinone (XXI), *2,3 - bis(5 - chloro - 2 - benzothiazolylthio) - 1,4 - naphthoquinone* (XXII), *2,3 - bis(6 - ethoxy - 2 - benzothiazolylthio) - 1,4 - naphthoquinone* (XXIII) *and diethyl 2,2′ - (1,4-dihydro - 1,4 - dioxo - 2,3 - naphthylenedithio)bis(4 - thiazolecarboxylate* (XXIV). To a stirred solution containing 0.2 mole of 2-mercaptobenzothiazole, 5-chloro-2-mercaptobenzothiazole, 6-ethoxy-2-mercaptobenzothiazole, or I, 13.2 g. (0.2 mole) of 85% potassium hydroxide, and 400 ml. of acetone, was added in one portion 23.7 g. (0.1 mole) of 2,3-dichloro-1,4-naphthoquinone.

The stirred reaction mixture was heated at 50–56° for 4 hr. and then added to 1500 g. of ice water. After stirring for 15 min., the solid was collected by filtration, washed with water until the washings were neutral to litmus, and air-dried at 25–30°. The data are summarized in Table VI.

Ethyl 4 - methyl - 5 - thiazolecarboxylate (XXV); *ethyl-4 - thiazolecarboxylate* (XXVI) *and 4 - methyl - 5 - thiazolecarboxylic acid* (XXVII). To a stirred slurry containing 0.5 mole of ethyl-2-mercapto-4-methyl-5-thiazolecarboxylate,[13] I or 2-mercapto-4-methyl-5-thiazolecarboxylic acid,[13] and 300 ml. of concd. hydrochloric acid at 50° was added dropwise 170 g. of 30% hydrogen peroxide over a 2-hr. period. During this addition an exothermic reaction set in and the temperature of the stirred reaction mixture was maintained at 50–75° by occasional cooling. The reaction mixture was stirred for an additional hour. For XXV and XXVI the stirred reaction mixture was cooled to 25° and filtered to remove the disulfides. To the stirred filtrate 245 g. of sodium carbonate was added in small portions until the *p*H of 8 was obtained. The stirred reaction mixture was extracted with 700 ml. of ethyl ether. The ether solution was dried over sodium sulfate and the ether was removed *in vacuo*. XXV was purified by distillation *in vacuo* and XXVI was recrystallized from heptane.

For XXVII the reaction mixture was added to 1000 g. of ice water. To this stirred slurry sodium carbonate was added in small portions until a *p*H 3.5 was obtained. The resulting solid was collected by filtration, washed with 400 ml. of water, and air-dried at 50°. The data are summarized in Table VII.

Acknowledgment. The writers wish to acknowledge their indebtness to R. O. Zerbe and D. D. Mullins for assistance rendered during the course of this investigation.

NITRO, W. VA.

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

Derivatives of Fluorene. X. Fluorofluorenes. III[1]

T. LLOYD FLETCHER, MOSES J. NAMKUNG, WILLIAM H. WETZEL, AND HSI-LUNG PAN

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Preparation of further monofluoro-2-acetamidofluorenes is described, completing the series for biological testing (carcinogenicity), together with new substances obtained in the course of this work. A further example of monodemethylation in the Schiemann decomposition of a dimethylamino-substituted molecule is observed.

In this paper we describe preparation of the two remaining monofluoro-(6- and 3-)-2-acetamidofluorenes and related compounds. These two, together with the four new isomers already reported, the 1-, 4-, 5- and 8-fluoro-2-acetamidofluorenes,[1,2] have been tested for toxicity and carcinogenicity

(1) *Fluorofluorenes. II., J. Org. Chem.*, **25**, 996 (1960). This work has been aided in part by a research grant (C-1744) from the National Cancer Institute, U.S.P.H.S. Part of this material was presented at the Chicago meeting of the American Chemical Society in September, 1958.

(2) T. L. Fletcher, W. H. Wetzel, M. J. Namkung, and H. L. Pan, *J. Am. Chem. Soc.* **81**, 1092 (1959).

by Drs. James A. and Elizabeth C. Miller.[3] The 7-fluoro isomer was synthesized and tested earlier.[4]

After submitting our latest report,[1] an article describing some of the products we have prepared has just appeared.[5] Some of these were obtained, admittedly, by methods in which they were minor by-products, very difficult to purify. We began this work with the idea[2] of devising practical syntheses which would give the relatively large amounts required for biological testing. It was stated in the publication[2] that we were embarked on a program of synthesizing the remaining monofluoro 2-acetamidofluorenes. The following and related papers[1,2] outline a quite different approach (from that in ref. 5) to the preparation of these substances.

The diazonium fluoborate of 3-aminofluorenone[6] was decomposed in toluene to give 3-fluorofluorenone. Here, as in previous work,[2] decomposition in sand gave less yield and poorer material. Nitration gave good yields of 3-fluoro-7-nitrofluorenone. Two reductions and acetylation led to the desired *N*-2-(6-fluorofluorenyl)acetamide.

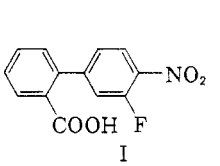
By diazotizing the supposed 3-fluoro-9-oxo-7-fluorenamine in fluoboric acid and decomposing the salt, we obtained 2,6-difluorofluorenone. For comparison the known 2-acetamido-3,7-dinitrofluorene[7] was oxidized, hydrolyzed and deaminated to give 3,7-(2,6-)dinitrofluorenone.[8] The latter was reduced with sodium sulfide to 2,6-diaminofluorenone.[8] Tetrazotization in the presence of fluoboric acid and decomposition gave 2,6-difluorofluorenone, identical with the above (melting point, mixture melting point and infrared spectrum).

N-2-(3-fluorofluorenyl)acetamide was made in two ways. In the better approach we simply nitrated 3-fluoro-7-trifluoroacetamidofluorene,[7] hydrolyzed the product for a few minutes in weak base[7] and deaminated it to give 3-fluoro-2-nitrofluorene. This was reduced and acetylated yielding the desired isomer, identical with the compound, whose structure we had already proved, prepared by the following laborious route.

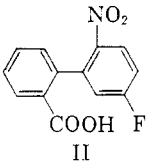
m-Fluoroaniline[9] was nitrated as described[10] giving mostly 3-fluoro-4-nitroaniline and a smaller amount of 3-fluoro-6-nitroaniline. The former was diazotized and treated with potassium iodide and iodine to give 3-fluoro-4-nitroiodobenzene which was coupled with a mixture of methyl *o*-chloro- and *o*-bromobenzoates (see Experimental) and worked up as usual. One of the by-products from symmetrical coupling, 3,3′-difluoro-4,4′-dinitrobiphenyl, was purified by sublimation.

When the crude carboxylic acid fraction of the foregoing reaction mixture was cyclodehydrated in polyphosphoric acid and extracted with alkali, a fluoronitrofluorenone was obtained. This was reduced with stannous chloride in hydrochloric acid (color characteristic of 2-aminofluorenone) and deaminated. The resulting fluorofluorenone was identical with 3-fluorofluorenone which we had already prepared.

A small amount of 1-fluoro-2-nitrofluorenone, the alternate cyclization product, was obtained during the purification of 2-amino-3-fluorofluorene (see I). This was identical[11] with a substance we described previously.[1]



I



II

It was conceivable, though hardly probable, that this minor product had come from a small amount of the lesser nitration isomer, 3-fluoro-6-nitroaniline, which in the subsequent series of reactions (see II) would have given 1-fluoro-4-nitrofluorenone. We therefore synthesized the latter compound, first from pure 3-fluoro-6-nitroaniline, and then from the known 1-amino-4-nitrofluorenone. Both procedures gave the same substance which was different from the by-product of the cyclization to the 2,3-isomer. Furthermore, deamination of the supposed 2-amino-1-fluorofluorenone gave 1-fluorofluorenone.

In another experiment we further confirmed the structure of the main Hodgson nitration product, 3-fluoro-4-nitroaniline, which could lead only to the 2,3- or 2,1-nitrofluorofluorenone. Diazotization of this aniline derivative in fluoboric acid and decomposition in chlorobenzene gave an oil which was fractionated. A yield of 24% of 2,4-difluoronitrobenzene was obtained, establishing the position of the nitro group as either 4- or 6-, with respect to $-NH_2$. Introduction of another nitro group gave the known 1,3-difluoro-4,6-dinitrobenzene (melting point mixture melting point and infrared spectrum). As we had made 1-fluoro-4-nitrofluorenone from the isomer with the nitro group *ortho* ot the amine (6-nitro), the main nitration product must necessarily have been as assumed.

(3) McArdle Memorial Laboratory, The University of Wisconsin.

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

(5) K. Suzuki, J. H. Weisburger, and E. K. Weisburger, *J. Org. Chem.*, **24**, 1511 (1959).

(6) N. Ishikawa, M. Okazaki, and M. Hayashi, *Yûki Gôsei Kagaku Kyokai-shi*, **15**, 34 (1958); *Chem. Abstr.*, **52**, 5349 (1958).

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

(8) N. Ishikawa and M. Hayashi, *Yûki Gôsei Kagaku Kyokai-shi*, **14**, 80 (1956); *Chem. Abstr.* **51**, 8049 (1957).

(9) (a) Purchased in part from L. Light and Company, England, (b) provided in part through the kindness of the Cancer Chemotherapy National Service Center, Bethesda 14, Maryland.

(10) H. H. Hodgson and D. E. Nicholson, *J. Chem. Soc.*, 766 (1941).

(11) See footnote 13 in reference 1.

The preceding is perhaps somewhat more confirmatory than necessary, but as described in the Experimental section we had prepared two derivatives of 4-nitro-3-fluoroaniline, neither of which agreed in melting point with compounds described in the literature,[10] although they both were analytically pure. We are at a loss to explain the discrepancy, but have not had opportunity to pursue the matter further.

Reduction of the 2-amino-3-fluorofluorenone to the corresponding fluorene and acetylation gave the 2,3-isomer, identical with the compound discussed above.

The Schiemann decomposition of 2-*N*,*N*-dimethylaminofluorene-1-diazonium fluoborate was shown[1] to give (31%) 2-*N*-monomethylaminofluorene as the only recognizable product. In the 2,3-series we attempted to confirm structure by making 2 - *N*,*N* - dimethylamino - 3 - fluorofluorene from known 2-*N*,*N*-dimethylamino-3-aminofluorene[12] and also by dimethylation of our supposed 2-amino-3-fluoro isomer. Here again the Schiemann decomposition failed, but gave some 2-*N*,*N*-dimethylaminofluorene with (probably) some *N*-monomethylaminofluorene.

We were curious about the reaction of the corresponding fluorenone. Diazotization in fluoboric acid and decomposition of the salt in boiling xylene led to 2-*N*-monomethylaminofluorenone in small yield.

We also prepared 2,4- and 1,3-difluorofluorenone (the 2,6- isomer was mentioned above). Decomposition of the diazonium fluoborate of 2-fluoro-9-oxo-2-fluorenamine gave an excellent yield of 2,4-difluorofluorenone.

Iodination of *m*-dinitrobenzene with fuming sulfuric acid and iodine[13] gave an improved yield (73%) of the 5-iodo derivative.[14] Reduction to 3-iodo-5-nitroaniline followed by a Schiemann reaction gave 3-fluoro-5-iodonitrobenzene. Further reduction to 3-fluoro-5-iodoaniline, diazonium fluoborate formation, and another decomposition gave us the known 3,5-difluoroiodobenzene. The structure of the latter compound was confirmed by nitration to 3,5-difluoro-2-nitroiodobenzene, identical with a compound obtained from 3,5-difluoro-2-nitroaniline. A specimen of the latter was generously donated.[15] An Ullmann condensation of 3,5-difluoroiodobenzene and a mixture of methyl *o*-bromo- and *o*-chlorobenzoates followed by the usual procedure and cyclodehydration in polyphosphoric acid gave 1,3-difluorofluorenone.

EXPERIMENTAL[16]

3-Fluorofluorenone. A mixture of 33 g. (0.169 mole) of 3-aminofluorenone and 400 ml. of 38% fluoboric acid was heated to form a salt and cooled to 5°. To the mixture, a saturated aqueous solution of 20 g. (0.29 mole) of sodium nitrite was added dropwise with stirring. After stirring a further 30 min., the diazonium salt was filtered and washed with cold 5% fluoboric acid, methanol, and ether and dried, 46 g. (93%), dec. 110°. The salt was decomposed by gently heating a suspension in 3 l. of toluene. We obtained 24.1 g. (72% based on the amine), m.p. 126–127°. One recrystallization from alcohol gave an analytical sample, m.p. 128.5–129°.

Anal. Calcd. for $C_{13}H_7FO$: C, 78.78; H, 3.56; F, 9.59. Found: C, 79.12; H, 3.61; F, 9.64.

3-Fluoro-7-nitrofluorenone. To 35 ml. of fuming nitric acid (d. 1.50) and 35 ml. of glacial acetic acid, 7 g. of 3-fluorofluorenone was added slowly at 35° with stirring. Concentrated sulfuric acid (7 ml.) was then added. The temperature of the mixture rose to 50° and it became a homogeneous solution. The stirring was continued for 10 min., while a light yellow substance precipitated. The reaction mixture was allowed to cool to room temperature, filtered, and washed with a small amount of cold glacial acetic acid and water, and dried, giving 7 g. (80.7%), m.p. 281–283°. An analytical sample was prepared by two recrystallizations from toluene, m.p. 282–283° (lit.,[5] m.p. 276–277°[17]).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.48; F, 7.81; N, 5.76. Found: C, 64.39; H, 2.41; F, 7.52; N, 5.77.

2-Amino-6-fluorofluorenone. A mixture of 19.2 g. (0.079 mole) of 2-nitro-6-fluorofluorenone, 80 g. (0.35 mole) of stannous chloride dihydrate, 80 ml. of concd. hydrochloric acid, and 40 ml. of ethanol was heated in a beaker. Reaction took place at the boiling point with evolution of gas. The mixture was boiled for 10 min. with stirring, then allowed to cool. The yellow precipitate was filtered, washed with water, and neutralized with aqueous ammonium hydroxide. The deep purple amine was washed with water, dried, and recrystallization raised the m.p. to 218–219°.

Anal. Calcd. for $C_{13}H_8FNO$: N, 6.57. Found: N, 6.49.

N-2-(6-Fluoro-9-oxofluorenyl)acetamide. Acetylation of the foregoing amine gave the amide. One recrystallization from toluene gave an analytical sample, m.p. 277–277.5°.

Anal. Calcd. for $C_{15}H_9FNO_2$: C, 70,58; H, 3.95, N, 5.49. Found: C, 70.54; H, 4.25; N, 5.32.

6-Fluoro-2-fluorenamine. A mixture of 11.7 g. of 2-amino-6-fluorofluorenone, 26 g. of red phosphorus, 35 ml. of 47% hydriodic acid, and 300 ml. of glacial acetic acid was refluxed for 40 hr. The reaction mixture was boiled down to small volume and diluted with 300 ml. of water. This was heated, filtered hot, and the filtrate neutralized with aqueous ammonium hydroxide. The resulting white precipitate was filtered, washed with water, and dried, giving 9.8 g. (90%), m.p. 123–125°. One recrystallization from benzene gave an analytical sample, m.p. 125–126° (lit.[5] m.p. 125–126°[17]).

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.02; N, 7.03. Found: C, 78.65; H, 5.22; N, 7.18.

N-2(6-Fluorofluorenyl)acetamide. The acetylation of the foregoing compound in benzene gave the acetyl derivative, m.p. 203–204° (lit.[5] m.p. 198–199°[17]).

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; F, 7.88; N, 5.81. Found: C, 74.84; H, 4.93; F, 7.66; N, 5.99.

2,6-Difluorofluorenone. (a) A mixture of 3.6 g. (0.017 mole) of 2,6-diaminofluorenone[8] and 30 ml. of 50% fluoboric acid was heated and then cooled to 0° in an ice-salt bath. To the mixture, a saturated aqueous solution of 3 g. (0.044 mole) of sodium nitrite was added dropwise with stirring over a period of 15 min. After a further 15 min. of stirring the diazonium salt was filtered and washed successively with

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

(13) C. F. H. Allen, H. W. J. Cressman, and H. B. Johnson, *Org. Syntheses*, **Coll. Vol. III**, 796 (1955).

(14) B. H. Nicolet, *J. Am. Chem. Soc.*, **49**, 1813 (1927).

(15) Dr. G. C. Finger, Illinois State Geological Survey, Urbana, Illinois.

(16) Melting points are corrected to standards and were taken on a Fisher-Johns block. Analyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(17) These literature melting points are uncorrected.

10 ml. of 5% fluoboric acid, 10 ml. of methanol, and 10 ml. of ether, and dried, giving 4.2 g. (70%) dec. 130°. Decomposition of the salt in 50 ml. of xylene, filtration, and evaporation of the xylene gave 1.7 g. (47%, based on the amine), m.p. 176–180°. One recrystallization from toluene (Darco) raised the m.p. to 184–185°.

(b) Diazotization of 6-fluoro-9-oxo-2-fluorenamine (2 g.) in a similar manner, in 15 ml. of 50% fluoboric acid and 25 ml. of 85% phosphoric acid, gave 2.9 g. (100%) of the diazonium salt, dec. 180°. Decomposition in *o*-dichlorobenzene gave 1.2 g. (33%) of the difluoro compound, m.p. 170–180°. One recrystallization from toluene (Darco) followed by sublimation under reduced pressure gave an analytical sample, m.p. 185–185.5°. A mixture melting point with the above showed no depression and the infrared spectra were identical.

Anal. Calcd. for $C_{13}H_6F_2O$: C, 72.22; H, 2.79; F, 17.59. Found: C, 72.24; H, 3.04; F, 17.39.

N-2-(6-Fluorofluorenyl)trifluoroacetamide. Trifluoroacetylation of 6-fluoro-2-fluorenamine with trifluoroacetic anhydride[18] in benzene gave this derivative, m.p. 187–188°; after one recrystallization from alcohol, it melted at 187.5–188°.

Anal. Calcd. for $C_{15}H_8F_4NO$: N, 4.74. Found: N, 4.94.

N-2(6-Fluoro-7-nitrofluorenyl)trifluoroacetamide. A solution of 34.8 g. (0.117 mole) of the foregoing compound in 350 ml. of glacial acetic acid was cooled to 60° and 35 ml. of nitric acid (d. 1.42) and 20 ml. of boron trifluoride(diacetic acid complex) were added. The temperature of the mixture rose to 75°, and after 10 min. began to diminish. The mixture was allowed to cool. The precipitate was filtered and washed with alcohol, giving 34 g. (85%), m.p. 286–289°. Two recrystallizations from toluene gave an analytical sample, m.p. 288–289°.

Anal. Calcd. for $C_{15}H_8F_4N_2O_3$: N, 8.23. Found: N, 8.26.

6-Fluoro-7-nitro-2-fluorenamine. To a suspension of 34 g. (0.1 mole) of the foregoing compound in 300 ml. of boiling ethanol 50 ml. of 5% aqueous sodium hydroxide was added. All the solids dissolved and the solution turned dark. After 5 min. of boiling, a dark red precipitate formed. Boiling was continued a further 10 min. and the mixture was cooled. The precipitate was filtered, washed with water, and dried, giving 24 g. (98.5%), m.p. 225–228°. Two recrystallizations from acetone-alcohol (1:1) gave an analytical sample, m.p. 232–233°.

Anal. Calcd. for $C_{13}H_9FN_2O_2$: C, 63.93; H, 3.72; N, 11.47. Found: C, 64.06; H, 3.91; N, 11.50.

2-Nitro-3-fluorofluorene. To a solution of 800 ml. of concd. hydrochloric acid and 14 g. (0.2 mole) of sodium nitrite at 0°, 20.5 g. (0.084 mole) of the foregoing compound was added in small portions with constant stirring. The mixture was stirred at −5° for 1 hr. and 800 ml. of precooled 50% hypophosphorous acid added. A large amount of gas evolved and the color of the solution became lighter. The stirring was continued for 5 hr. at this temperature and the mixture was stored in a refrigerator overnight. It was then warmed on a water bath for 1 hr. and the light brown precipitate filtered, washed with water, and dried, giving 14.9 g., m.p. 125–135°. Recrystallization from ethanol (Darco) gave 12.5 g. (66%), m.p. 131–135°. Recrystallization from benzene and then from ethanol gave an analytical sample, m.p. 134.5–135° (lit.[5] m.p. 134.5–135.5°[17]).

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52; F, 8.30; N, 6.11. Found: C, 68.38; H, 3.45; F, 8.44; N, 6.13.

3-Fluoro-2-fluorenamine. Reduction of 11.5 g. of the foregoing compound in 500 ml. of toluene and 100 ml. of ethanol with Raney nickel and 10 ml. of hydrazine hydrate[12] gave 10.0 g. (96.5%) of the amino compound, m.p. 129–130.5°. A mixture melting point with 3-fluoro-2-fluorenamine was undepressed (lit.[5] m.p. 131–131.5°[17]).

(18) Provided through the kindness of the Cancer Chemotherapy National Service Center, Bethesda 14, Maryland.

Acetylation gave the amide identical with *N*-2-(3-fluorenyl)acetamide which is described below.

3-Fluoro-4-nitroaniline. This compound was prepared by both reported methods.[10] After two recrystallizations from benzene it melted at 158.5–159.5° (lit.,[10] m.p. 153°).

3-Fluoro-4-nitro-iodobenzene. Diazotization of 19.8 g. of 3-fluoro-4-nitroaniline and replacement of the diazonium group with iodine (with the use of potassium iodide and iodine) gave 32 g. of crude iodo compound. Recrystallization from ethanol (Darco) gave 28.5 g. (84%), m.p. 118–118.5°.

Anal. Calcd. for $C_6H_3FINO_2$: C, 26.99; H, 1.13; I, 47.54. Found: C, 27.27; H, 1.23; I, 47.33.

3-Fluoro-2-nitro-9-oxofluorenone. An Ullmann coupling procedure using 16.2 g. (0.061 mole) of 3-fluoro-4-nitroiodobenzene with a mixture[19] of 17.1 g. (0.1 mole) of methyl *o*-chlorobenzoate, 21.8 g. (0.1 mole) of *o*-bromobenzoate was run in a 200-ml. round-bottom flask equipped with stirrer, air condenser, and a stoppered wide tube. Activated copper powder[20] (100 g.) was added gradually (1 hr.) through the short tube, removing the stopper as briefly as possible, and with very rapid stirring. The bath temperature was kept at 218° and the stirring was continued 1 hr. after all the copper had been added. After cooling, the mixture was extracted with acetone and the combined extracts from four batches were boiled down to a red oil and hydrolyzed.[21] The green crystalline product was boiled in 600 ml. of water with 120 g. of sodium carbonate (Darco), and the mixture was cooled and filtered. The precipitate was extracted with benzene and the latter was boiled down almost to dryness and the residue extracted with ligroin (d. 0.67–0.69). The residue from ligroin evaporation, 0.94 g., was sublimed under reduced pressure to give 0.52 g. of 3,3′-difluoro-4,4′-dinitrobiphenyl, m.p. 196–198°. Recrystallization from methanol raised the melting point to 197.5–198.5°.

Anal. Calcd. for $C_{12}H_6F_2N_2O_4$: F, 13.56; N, 9.99. Found: F, 13.17; N, 10.10.

The basic filtrate from the separation of the foregoing was heated to boiling and cautiously acidified with concd. hydrochloric acid to give 76.5 g. of green crystals which were mixed with 400 g. of polyphosphoric acid and heated in an oven (155°) for 3 hr. with occasional stirring. The cooled mixture was poured over ice with thorough stirring and filtered. The solid material was boiled in 600 ml. of water with 70 g. of sodium carbonate and, after cooling, filtration gave 4-carboxyfluorenone in the filtrate. Acidification and recrystallization gave 8 g. of 4-carboxyfluorenone, m.p. 222–223°.

The dark yellow residue from this separation was recrystallized from 300 ml. of ethyl acetate (Darco) giving 14.2 g. of yellow crystals, m.p. 220.5–222.5°; a second crop amounted to 3.4 g., m.p. 217–221.5° (total 30%). The combined crops, after recrystallization from ethyl acetate (Darco), gave 15.8 g. of the fluorenone, m.p. 222–223°. As shown in the following paragraphs, this contained some of 2,1- isomer. An analytical sample from chloroform from a further preparation melted at 224–224.5° (lit.[5] 220–221°[17]).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49; F, 7.81; N, 5.76. Found: C, 64.25; H, 2.63; F, 7.56; N, 5.67. Mol. wt. Calcd.: 243. Found: 235.

2-Amino-3-fluorofluorenone. Reduction of 15.8 g. of the above with stannous chloride and hydrochloric acid[22] gave the amine (13.5 g.) as bright red crystals. Recrystallization from benzene gave a first crop of 9.8 g. (70%), m.p. 163–164.5°. One more crystallization from benzene raised this to

(19) This empirical mixture gave us a better yield than either *o*-halo ester alone, in a considerable number of trials.

(20) See footnote 16 in reference 2.

(21) M. S. Lesslie and E. Turner, *J. Chem. Soc.*, 1760 (1930).

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

168–169°. A small sample of this was acetylated and after recrystallization from ethanol it melted at 262–263°.

Anal. Calcd. for $C_{15}H_{10}FNO_2$: C, 70.58; H, 3.95; F, 7.44; N, 5.49. Found: C, 70.74; H, 4.08; F, 7.31; N, 5.60.

The mother liquor from the first crop of the 2,3-fluoroamino compound gave more of that isomer and 1.2 g. (9%) (after benzene recrystallization) of *2-amino-1-fluorofluorenone*, m.p. 129–130.5°, still containing some of the 2,3 isomer (infrared spectrum).

Anal. Calcd. for $C_{13}H_8FNO$: N, 6.57. Found: N, 6.68.

Reduction with phosphorus and 47% hydriodic acid (48 hr.) gave a product which, after several crystallizations proved to be the same compound we have already reported[1] as 1-fluoro-2-fluorenamine. Acetylation gave us the amide, m.p. 187–188° (lit.,[1] m.p. 182–183°, 180.5–181.5°[5,17]).

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67, H, 5.01; F, 7.88; N, 5.81. Found: C, 74.50; H, 5.04; F, 7.70; N, 5.70.

A mixture melting point with the 2,1 isomer that we reported[1] was 186–188° (with slight softening). A mixture of 80% of the 2,1-acetamido isomer[1] with 20% of the 2,3-isomer (see above) melted at 186.5–188°, and a mixture melting point of this combination with the sample melting 187–188° showed no depression. The infrared spectrum[23] was identical with the 2,1-isomer except for hints of five bands all of which could be found in the spectrum of the pure 2,3-isomer.

Deamination of the above 2-amino-1-fluorofluorenone with hypophosphorous acid gave a crude product which was chromatographed on alumina (benzene). The principal substance from the eluate was recrystallized from *n*-heptane, m.p. 110–112°. A mixture melting point with authentic 1-fluorofluorenone showed no depression.

3-Fluoro-2-fluorenamine. Reduction of 3-fluoro-9-oxo-2-fluorenamine (3.6 g.) with phosphorus and 47% hydriodic acid gave 85% of crude product. After two recrystallizations from ligroin (d. 0.72–0.74), the compound melted at 130–131°. A mixture melting point with the compound described above from the alternate method was not depressed (lit.,[5,17] m.p. 131–131.5°).

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.02; N, 7.03. Found: C, 78.51, H, 5.25, N, 7.11.

Acetylation and recrystallization from benzene gave 2-acetamido-3-fluorofluorene, m.p. 198.5–199.5° identical (melting point, mixture and infrared spectrum[23]) with the compound already described (lit.,[5,17] m.p. 194–195°).

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; F, 7.88; N, 5.81. Found: C, 74.69; H, 5.24; F, 7.81; N, 5.59.

Deamination of 3-fluoro-9-oxo-2-fluorenamine. A small quantity of this ketone was deaminated in the usual way with hypophosphorous acid. The crude product was sublimed under reduced pressure and recrystallized from ethanol, m.p. 125.5–127°. A mixture melting point with 3-fluorofluorenone was not depressed.

1-Fluoro-4-nitrofluorenone. (a) The by-product in the nitration of *m*-fluoroaniline, 3-fluoro-6-nitroaniline,[10] was diazotized and the diazonium group replaced with iodine. This iodo compound, obtained as an oil, was carried through the Ullmann reaction and worked up as described above. After cyclodehydration a small yield of a substance, m.p. 168.5–170° was obtained. A mixture melting point with 1-fluoro-4-nitrofluorenone showed no depression [see (b)].

(b) 1-Amino-4-nitrofluorenone[24] (3.47 g.) was diazotized in fluoboric acid and the dried salt (quant.), dec. 151°, was decomposed in 100 ml. of bromobenzene at a temperature of 130° gradually rising to 155° in 2 hr. The mixture was then boiled (Darco) and filtered. After evaporation of the solvent under reduced pressure, the product was purified by chromatography on alumina (benzene). A fraction, m.p. 160–168°, was recrystallized from acetone and alcohol (1:1) to give 1.05 g. (30%), m.p. 165.5–168°. An analytical sample, m.p. 172.5–173.5°, was prepared by two recrystallizations from ethyl acetate.

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49; F, 7.81. Found: C, 64.05; H, 2.47; F, 7.58.

A mixture with the product in a) gave m.p. 169–170.5° with no prior softening.

Establishment of the structure of the principal nitration product of m-fluoroaniline. Diazotization of the supposed 3-fluoro-4-nitroaniline in fluoboric acid and decomposition of the salt in hot chlorobenzene 90–130° was followed by fractionation, first to remove the solvent; refractionation led to a compound (2,4-difluoronitrobenzene) boiling at 85–86° (11 mm.) which at this stage amounted to 24%, based on the amine. Nitration of the latter (0.30 g.) gave 0.35 g. of 1,3-difluoro-4,6-dinitrobenzene, m.p. 73–74°. A mixture melting point with the authentic material,[9a] m.p. 73–74°, was not depressed. The infrared spectra of the two substances were identical. The main product of nitration must therefore have been as assumed.

Derivatives of 3-fluoro-4-nitroaniline. (a) 3-Fluoro-4-nitrophenol was prepared as reported,[10] m.p. 91.5–92.5° (lit.,[10] m.p. 42°). None of the other three isomeric fluoronitrophenols is reported to melt near 90°.

Anal. Calcd. for $C_6H_4FNO_3$: C, 45.87; H, 2.56; N, 8.92. Found: C, 45.51; H, 2.68; N, 9.04.

(b) *3-Fluoro-4-nitroacetanilide* was also prepared,[10] m.p. 175–176° lit.,[10] m.p. 140°.

Anal. Calcd. for $C_8H_7FN_2O_3$: N, 14.14. Found: N, 14.13.

2-N,N-Dimethylamino-3-fluorofluorene. 2-Amino-3-fluorofluorene (1 g.) and trimethyl phosphate (0.5 g.) were mixed and heated at 190–195° (bath) for 1.5 hr. The reaction mixture was boiled for 5 min. in a solution of sodium hydroxide (0.9 g.) in water (3 ml.) then cooled. After dilution with water (15 ml.) the solid mass was pulverized, filtered, washed with water, and dried. Recrystallization from ethanol (Darco) gave shiny plates (0.8 g.). Three recrystallizations from methanol gave an analytical sample, m.p. 109–110°.

Anal. Calcd. for $C_{15}H_{14}FN$: C, 79.27; H, 6.21; N, 6.16. Found: C, 79.39; H, 6.04; N, 6.35.

Decomposition of 2-N,N-dimethylamino-3-fluorenediazonium fluoborate. Diazotization of 2-*N*,*N*-dimethylamino-3-fluorenamine[12] in the usual way in fluoboric acid gave a salt (dec. ~130°). This was decomposed in boiling xylene to give 1.6 g. (from 2.9 g. of the amine), m.p. 80–115°. Fractional crystallization from petroleum ether and from methanol finally yielded a small amount of 2-*N*,*N*-dimethylaminofluorene (mixture melting point) and a crude fraction which appeared to be largely 2-*N*-monomethylaminofluorene. We were not able to isolate any material which corresponds to the fluoro derivative described in the preceding paragraph.

2-N,N-Dimethylamino-3-fluorofluorenone. 2-Amino-3-fluorofluorenone (1 g.) was dissolved in trimethyl phosphate (1.3 g.) by heating. The solution was cooled somewhat and powdered anhydrous lithium bromide[25,26] (0.82 g.) was added in one portion. The mixture was shaken and heated under reflux at 120–125° (bath) for a few minutes then at 135–140° (bath) for 1 hr. The bath temperature was raised to 140–145° and heating was continued for 0.5 hr. The pasty reaction mixture was boiled for 20 min. in a solution of sodium hydroxide (0.5 g.) in water (5 ml.) and stirred into cold water. After filtration and washing the dry precipitate weighed 0.9 g. Recrystallization from carbon tetrachloride–methanol gave 0.62 g., m.p. 94.5–95.5°. One more recrystallization from methanol raised the melting point to 95.5–96.5°.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; F, 7.88; N, 5.81. Found: C, 74.54; H, 4.62; F, 7.81; N, 6.00.

2-N,N-Dimethylamino-9-oxo-3-fluorenamine. Reduction[22] of 2-dimethylamino-3-nitrofluorenone[7] (8.05 g.) yielded 2 g.

(23) Beckman IR-5; potassium bromide disc.

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

(25) T. L. Fletcher, M. E. Taylor, and A. W. Dahl, *J. Org. Chem.*, **20**, 1021 (1955).

(26) See footnote e, Table I, in reference 12.

(28%) of the amine, m.p. 172.5–173.5°. This proved difficult to purify. After several crystallizations from 50% ethanol and from methanol a sample was obtained, m.p. 174–175°.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92. Found: C, 75.21, H, 5.53.

Decomposition of 2-N,N-dimethylamino-9-oxo-3-fluorenediazonium fluoborate. The amine (2 g.) was diazotized in the usual way giving 3.2 g. of the red salt, dec. 124°, which was ground to a powder and decomposed in a xylene (120 ml.) suspension by gradually increasing the temperature to the boiling point (0.5 hr.) and boiling gently for 1.5 hr. with replacement of the solvent lost by evaporation. The mixture was cooled to 0° and the solvent decanted from the purple product. After warming and evaporating, the remaining solvent in a current of air the solid was triturated with 5% ammonium hydroxide solution, which was boiled briefly, filtered, washed, and dried. It was then dissolved in a few ml. of benzene and chromatographed on alumina and was eluted with a 4:1 mixture of benzene and ethanol. The crude product was wide-melting. After crystallizations from benzene (once) and methanol (twice), a sample was obtained melting at 157.5–158.5°. A mixture melting point with authentic 2-*N*-monomethylaminofluorenone showed no depression.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36, H, 5.30, N, 6.69. Found: C, 80.61; H, 5.10; N, 6.81; F, 0.00.

2,4-Difluorofluorenone. 2-Amino-4-fluorofluorenone (0.5 g., 0.0023 mole) was mixed with 48% fluoboric acid (15 ml.) and cooled to 0°. The mixture was diazotized with a solution of sodium nitrite (0.2 g., 0.0029 mole) in water (1 ml.). After 30 min. of stirring, the diazonium fluoborate was filtered, washed, and dried. It was then mixed with four times its volume of sand and decomposed under reduced pressure at 170–185° (20 min.). The difluoro- compound was extracted with benzene and a small portion was sublimed under reduced pressure at 155–160° giving shiny yellow leaflets, m.p. 144.5–145.5°.

Anal. Calcd. for $C_{13}H_6F_2O$: C, 72.22; H, 2.80; F, 17.58. Found: C, 72.33; H, 2.81; F, 17.36.

The remaining product was chromatographed on alumina (benzene). One recrystallization from aqueous methanol gave 0.35 g., m.p. 143–144°. The total yield was 85–90%.

1,3-Dinitro-5-iodobenzene. This known[14] compound was made by the following improved procedure: In a 2-l. flask, fitted with a reflux condenser, *m*-dinitrobenzene (125 g., 0.745 mole), fuming sulfuric acid (500 ml., 20–30%), and iodine (97 g., 0.382 mole) were mixed. The temperature was allowed to rise slowly, during 1 hr., to 150° (bath) with occasional shaking. White fumes arose from the reflux condenser. Heating was continued (150–155°) until the evolution of white fumes diminished. Occasionally, during the reaction, a little fuming sulfuric acid was added to wash down the sublimed iodine which had collected on the sides of the condenser. The contents were cooled to about 50° and poured over ice cubes with stirring. The mixture was transferred to a mortar and the solid product ground to fine particles. It was then filtered, washed well with water, dried, and recrystallized from 500 ml. of absolute ethanol to give 160 g. (73%) of 1,3-dinitro-5-iodobenzene, m.p. 99–100°. One more recrystallization gave m.p. 99.5–100.5° (lit.,[14] m.p. 99°).

3-Iodo-5-nitroaniline. Sodium sulfide (120 g.) and sulfur (30 g.) were added to 450 ml. of water and warmed until the solution became clear. This was added through a dropping funnel over a period of 1.5 hr. to a boiling, mechanically-stirred solution of 128.3 g. of 1,3-dinitro-5-iodobenzene and 600 ml. of water in a 2-l. beaker. After the addition, the mixture was heated for 0.5 hr. longer with stirring, cooled by adding ice, and the precipitated product filtered off. The latter was boiled for 45 min. in a mixture of 450 ml. of water and 105 ml. of concd. hydrochloric acid. After cooling slightly it was filtered through a sintered glass funnel of medium porosity. The extraction was repeated and the combined filtrates were neutralized with concd. ammonium hydroxide, cooled, and the precipitate recovered by filtration. The dried product was recrystallized from 300 ml. of 95% ethanol (Darco) and boiled down to 150 ml. The first crop, amounting to 40 g., melted at 135.5–139° (35.4%), and was used at this stage in the next step. A second crop yielded 10 g., m.p. 132–135°.

The analytical sample was obtained by two recrystallizations from ethanol, m.p. 140–141°.

Anal. Calcd. for $C_6H_3IN_2O_2$: N, 10.61. Found: N, 10.76.

3-Iodo-5-nitrobenzenediazonium fluoborate. 3-Iodo-5-nitroaniline (35 g., 0.133 mole) was added to 87.5 ml. of 48–50% fluoboric acid diluted with 125 ml. of water. The mixture was stirred magnetically, cooled to 5–10° in an ice bath, and 9.3 g. (0.135 mole) of sodium nitrite in 52 ml. of water was added dropwise over a period of 20 min. It was stirred for an additional 20 min., filtered, and washed successively with 90 ml. of cold 5% fluoboric acid, 26 ml. of cold methanol, and three 50-ml. portions of ethyl ether. The tan product was dried in a desiccator giving 46 g. (95.4% of the diazonium salt, dec. 155–166°.

3-Fluoro-5-iodonitrobenzene. The diazonium salt 50 g. (0.138 mole) was decomposed by mixing with an equal volume of dry sand in a 500 ml. flask heated in a wax bath at 140° under aspirator vacuum. The temperature was slowly raised to 150°, at which point steady decomposition took place during 1 hr. The cooled mixture was then extracted with 95% ethanol. The extracts were combined and boiled with Darco and then filtered. Hot water was added to the boiling filtrate, to the point of cloudiness, to give a crude product, m.p. 64–76°. Combined yields of six such decompositions gave 115 g. The latter was purified by extracting with 350 ml. of 50% aqueous acetic acid. The extract was boiled until only a reddish-brown oil remained and the clear solution allowed to cool and solidify. The yield was 89 g. (40%), m.p. 75.5–78°.

An analytical sample was obtained by recrystallizing once from aqueous ethanol and twice from petroleum ether (b.p. 30–60°), m.p. 77–78.5°.

Anal. Calcd. for $C_6H_3FINO_2$: C, 27.00; H, 1.13; N, 5.25. Found: C, 26.89; H, 1.53; N, 5.05.

3-Fluoro-5-iodoaniline. Two 45-g. batches of 3-fluoro-5-iodonitrobenzene were reduced with stannous chloride and hydrochloric acid in the usual way.[22] After the sodium hydroxide treatment of the crude mixture, the alkaline solution was extracted twice with 500-ml. portions of ether. A small sample of the ether solution was removed, dried, and boiled down to give the amine as an oil. Addition of acetic anhydride gave a product which was recrystallized twice from aqueous ethanol, once from benzene, and once from benzene and cyclohexane (1:1). We thus obtained an analytical sample, m.p. 154–156°, of *3-fluoro-5-iodoacetanilide.*

Anal. Calcd. for C_8H_7FINO: C, 34.43; H, 2.53; F, 6.81; N, 5.02. Found: C, 34.68; H, 2.53; F, 6.79; N, 4.83.

The remainder of the ethereal solution of the free amine was dried and the ether evaporated. During the last part of the evaporation 150 ml. of 50% fluoboric acid were slowly added. After further heating on the steam bath and cooling, crystals were obtained which were dried by suction (110 g., dec. 183–191°). This entire product was added to 110 ml. of 50% fluoboric acid in 100 ml. of water and cooled to 5–10°, diazotizing with sodium nitrite (23.4 g., 0.34 mole) in 50 ml. of water to give a thick pink slurry. After stirring for an additional 45 min., the mixture was filtered, washed with 150 ml. of 5% cold fluoboric acid in several portions, two 35-ml. portions of cold methanol and finally with 50 ml. of ether. After drying, the pink precipitate weighed 64.3 g. (56.5%), dec. 141°.

1,3-Difluoro-5-iodobenzene. The entire amount of the diazonium salt was decomposed in two portions under reduced pressure (17 mm.), each mixed with an equal volume of sand, at a temperature range of 135–160° for 1.5 hr. The crude liquid product, which distilled, was collected in a cooled receiver and amounted to 42 g. This was fractionated

to give 36 g. (79%) of 3,5-difluoroiodobenzene, b.p. 58–60° (17 mm.).

Anal. Calcd. for $C_6H_3F_2I$: C, 30.03; H, 1.26; F, 15.83; I, 52.88. Found: C, 30.23; H, 1.17; F, 15.61; I, 52.68.

This substance was reported[27] as obtained from Dr. G. C. Finger.[15] The structure was confirmed by nitration with fuming nitric acid (d. 1.50) and sulfuric acid at −5°. After pouring onto ice and filtering, a 96.5% yield of 3,5-difluoro-2-nitroiodobenzene was obtained, m.p. 66.5–67.5°. An analytical sample was obtained upon recrystallization from petroleum ether (b.p. 40–60°), m.p. 66.5–67.5°.

Anal. Calcd. for $C_6H_2F_2INO_2$: N, 4.92. Found: N, 5.06.

The amine group of 3,5-difluoro-2-nitroaniline[15] was replaced in the usual way with iodine. This was identical with the sample obtained above (melting point and mixture melting point).

1,3-Difluorofluorenone. A mixture of 8 g. of 1,3-difluoro-5-iodobenzene, 11 g. of methyl *o*-bromobenzoate, and 11 g. of methyl *o*-chlorobenzoate was treated (rapid stirring) with 50 g. of activated copper (added gradually) at a temperature of 200–210° over a period of 1.5 hr. Stirring was continued after the addition, for 0.5 hr., at a bath temperature of 215–218°. The product was obtained from the reaction mixture in the usual way with the cyclodehydration step carried out in polyphosphoric acid. A crude yield of 1.65 g. of the ketone was obtained. Chromatography of 0.2 g. of this material through alumina (benzene) gave two zones. From the faster moving band, light yellow leaflets were obtained. Recrystallization from methanol gave 0.09 g., m.p. 188–189°. The same material was also obtained by subliming the crude product at 130–145° (bath) at 1 mm.

Anal. Calcd. for $C_{13}H_6F_2O$: C, 72.22; H, 2.80; F, 17.58. Found: C, 72.44; H, 2.94; F, 17.61.

From the slower-moving band there was obtained 0.03 g. of a yellow compound, m.p. 224.5–225.5°, which did not sublime at 145° (1 mm.).

Anal. Found: F, 10.46.

Further characterization has not been attempted.

SEATTLE 5, WASH.

(27) H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *J. Am. Chem. Soc.*, **74**, 4809 (1952).

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

Derivatives of Fluorene. XI. New Nitrogen Mustards[1]

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Some *N*-fluorenyl nitrogen mustards postulated to give more or less tendency for ethylenimmonium ion formation have been designed. The ultraviolet spectra of these and related compounds have been determined, in both neutral and acidic solutions, with a view to studying quaternization (ethylenimmonium ion formation) and in order to correlate these data with possible biological activity. No ethylenimmonium ion formation occurs in most of the compounds reported and protonation of the amine nitrogen is achieved more readily with the amino, dimethylamino, or diethylamino groups than with the mustard group. It is tentatively concluded that a fluorene nitrogen mustard, properly substituted with strong electron donor groups, might exist, at least partially, in the ethylenimmonium ion form.

Prior to this work,[2] only two nitrogen mustard derivatives of fluorene have been reported in the literature, 2-*N*,*N*-di-(β-chloroethyl)aminofluorene[3] and its bromo analogue.

In view of the interesting biological effects of many nitrogen mustards, the variety of biological effects of many substituted fluorenes and the fact that 2-aminofluorene and a number of its derivatives are carcinogenic, we have synthesized a group of *N*,*N*-di-(β-chloroethyl)aminofluorenes and related substances for their own chemical and biological interest and as a background for further specifically tailored nitrogen mustards to be reported on shortly. We were interested in learning the effects of certain changes in the availability of the extra electron pair of the nitrogen atom of the mustard moiety, chemically, spectrally, and ultimately biologically. It was recently suggested[4] that certain structural devices—for example, hydrogen bonding with the electron pair of this nitrogen—would tend to stabilize the β-chloroethylamine form, thus retarding formation of the ethylenimmonium ion and prolonging or potentiating physiological activity of the compound *in vivo*. We felt that this same general purpose could be effected in a series of compounds with the fluorene nucleus properly substituted with electron attracting or electron donating groups. For example, in the case of 2- *N*,*N*-di(β-chloroethyl)amino-7-nitrofluorene the electronegative nitro group would lower the availability of the electron pair on the amine nitrogen and thus inhibit quaternization.

Some of the di-β-hydroxy compounds (See Table I) were prepared by the reaction of ethylene oxide in dilute acetic acid at elevated temperatures and pressures in a bomb. As poor yields resulted with certain amines, the method of bis-β-hydroxyethylation at room temperature[5] was adopted.

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(2) Some of the material was presented at the meeting of the American Chemical Society, New York, September 1957.

(3) W. Davis, J. L. Everett, and W. C. J. Ross, *J. Chem. Soc.* 1331 (1950).

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(5) F. Bergel and J. A. Stock, *J. Chem. Soc.*, 2409 (1954).