SECTION C
Organic Chemistry

Fluorenylhydroxamic Acids Isomeric with the Carcinogen *N*-Fluoren-2-ylacetohydroxamic Acid. Part I. Synthesis of *N*-Fluoren-1-yl-, *N*-Fluoren-3-yl-, and *N*-Fluoren-4-ylacetohydroxamic Acid

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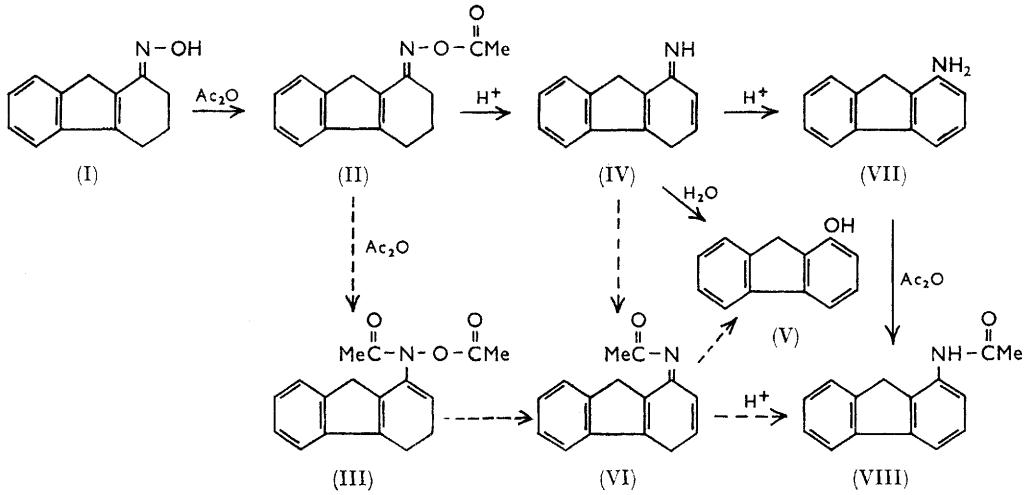
Three new fluorenylhydroxamic acids isomeric with the carcinogen *N*-fluoren-2-ylacetohydroxamic acid have been synthesized by partial catalytic reduction of the corresponding nitrofluorenes, prepared in turn by oxidation of the respective fluorenamines with peroxymaleic acid. A route to *N*([1-^{14}C]fluoren-1-yl)acetamide and -acetohydroxamic acid by aromatization of the oxime of 3,4-dihydrofluoren-1(2*H*)-one by the Semmler–Wolff rearrangement has been explored. Analysis of the products by t.l.c. indicated the imine as an intermediate when this oxime was rearranged in the presence of limited amounts of acetic anhydride.

RECENT evidence indicates that the carcinogenicity of *N*-fluoren-2-ylacetamide is due to its metabolic conversion to *N*-fluoren-2-ylacetohydroxamic acid.[1] To determine whether carcinogenicity is a general property of fluorenylhydroxamic acids, the positional isomers, *N*-fluoren-1-yl-, *N*-fluoren-3-yl-, and *N*-fluoren-4-ylacetohydroxamic acid and some derivatives were prepared by the partial catalytic reduction of the corresponding nitrofluorenes. The latter compounds were obtained by oxidation of the respective fluorenamines with peroxymaleic acid. Fluoren-1- and -4-amine were made by Huang-Minlon reduction[2] of the corresponding aminofluorenones. Reduction of 3-nitrofluoren-9-one by the same method gave fluoren-3-amine in one step (70—90%). The previous method required two successive reductions.[3]

Oxidation of the fluorenamines with peroxymaleic acid in methylene chloride afforded the nitrofluorenes [38% (average of 22 oxidations), comparable to the yield reported for the oxidation of 2-naphthylamine with peroxymaleic acid (40%)[4]; yields varied from 60 to 20%]. The hindered fluoren-4-amine, when oxidized at 0°, gave 4-nitrosofluorene (40%). The formation of 4-nitrosofluorene confirmed previous work on the oxidation of hindered amines by peracetic acid.[5] The solubility of peroxymaleic acid in methylene chloride (by titration[6]) was only 0·15% (w/w); most of the peroxymaleic acid was present in the lower layer which forms when hydrogen peroxide is added to maleic anhydride in methylene chloride. Efficient stirring during the oxidation is therefore essential. Maleamic acids arising from acylation of the amines with unchanged maleic anhydride were the major by-products. Use of low molar ratios of peroxyacid to fluorenamine



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[2] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[3] F. E. Ray and J. G. Barrick, *J. Amer. Chem. Soc.*, 1948, **70**, 1492; E. K. Weisburger, *ibid.*, 1955, **77**, 1914.
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[5] R. R. Holmes and R. P. Bayer, *J. Amer. Chem. Soc.*, 1960, **82**, 3454; H. R. Gutmann, *Experientia*, 1964, **20**, 128.
[6] G. Braun, *Org. Synth.*, Coll. Vol. I, 1941, 434; F. P. Greenspan and D. G. MacKellar, *Analyt. Chem.*, 1948, **20**, 1061.

yielded azoxyfluorenes; use of high molar ratios gave fluorenones.

An alternative route to fluoren-1-amine, designed to incorporate ^{14}C into a metabolically stable position within the fluorene system,[7] involved the reactions devised by Howell and Taylor which lead to 3,4-dihydrofluoren-1(2*H*)-one. The intermediate, 3-inden-3-ylpropyl bromide, which had previously been separated by distillation,[8] contained small amounts of 3-inden-3-ylpropanol. Chromatography on alumina yielded the pure halide and a new by-product, bis-[3-(inden-3-yl)propyl] ether. Production of the latter was virtually eliminated when pyridine was present during the bromination of 3-inden-3-ylpropanol. The oxime of 3,4-dihydrofluoren-1(2*H*)-one (I),[9] when subjected to a Semmler–Wolff aromatization [10] with a 20-fold excess of acetic anhydride, gave *N*-fluoren-1-ylacetamide (VIII) (80—90%). Although the mechanism of this rearrangement has not been fully elucidated, there is evidence that the reaction proceeds through an imine.[11] In a somewhat different mechanism an imide, presumed to arise from a hypothetical *NO*-diacetylhydroxylamine, was proposed as an intermediate.[12] To clarify which of these mechanisms applies to the aromatization of (I), the reaction was carried out with limited amounts of acetic anhydride (1·5 mol.) T.l.c. of the basified reaction mixtures disclosed the presence of fluoren-1-ol (V), which was converted into the benzoate. This product (V) arose from the addition of water to the intermediate imine (IV) or imide (VI) and the subsequent loss of ammonia or acetamide, respectively. The figure shows the amounts of (V) [which reflects the amounts of (IV) and/or (VI) in the reaction mixture] and those of fluoren-1-amine (VII) and *N*-fluoren-1-ylacetamide (VIII) present at various times. These data were compatible with the formation of either (IV) or (VI) as intermediates in the aromatization. The decline in the concentration of fluoren-1-ol, the product of hydrolysis of (IV) or (VI), agreed with the view that (IV) and/or (VI) was the precursor of (VII) and (VIII). Quantitative analysis indicated that the pathway involving (IV) is the major route for the aromatization of (I), when the amount of acetic anhydride is limited. According to the data of Table 2, the amine (VII) comprised 67% of the aromatized end-products. Since (IV) was considered to be the immediate precursor of (VII), the quantities of (IV) formed in the reaction were at least double the amounts of (VI). The formation of (VIII) by the alternate pathway involving (III) and (VI) would be expected to be increased when a large excess of acetic anhydride is employed. However, the contribution of this pathway to the formation of (VIII) cannot be determined experimentally; spectrophotometric measurements showed that (VII) in acetic acid saturated with hydrogen chloride, when treated with 20-fold excess of acetic anhydride, was acetylated to the extent of 80—100%.

EXPERIMENTAL

M.p.s. were taken with a Fisher–Johns apparatus. I.r. spectra were recorded with a Beckman IR-10 or IR-4 spectrophotometer and u.v. spectra with a Beckman DK-2 spectrophotometer. N.m.r. spectra were obtained with a Varian-A60 spectrometer with tetramethylsilane as internal reference. Silica gel GF_{254} for t.l.c. was obtained from Brinkmann Instruments, Inc., 90% hydrogen peroxide from the Shell Chemical Co., and 1-amino-, 4-amino-, and 3-nitrofluoren-9-one from Aldrich Chemical Company.

3-(*Inden-3-yl*)*propyl Bromide*.—To a solution of 3-(inden-3-yl)propanol (4·63 g., 0·266 mole) in benzene (240 ml.) were added pyridine (2·1 ml.) and sodium bromide (1·0 g.). Phosphorus tribromide (10·1 ml., 0·106 mole) in benzene (35 ml.) was then added dropwise and the suspension was stirred at 62° for 17 hr. The mixture was then washed with water (300 ml.), dilute sodium acetate (2 × 100 ml.), and water. The benzene solution was dried ($MgSO_4$) and the solvent was evaporated off. The oily residue (60·6 g.), n_D^{20} 1·5946, was chromatographed on alumina (neutral grade; 266 g.) with n-hexane as eluant. The first yellow band to emerge yielded the halide as an oil (42·1 g., 72·5%), n_D^{20} 1·5900. A portion was distilled at 116°/0·35 mm., the product had n_D^{20} 1·5894 (lit.,[8] n_D^{20} 1·5851) (Found: C, 60·5; H, 5·55; Br, 33·65. Calc. for $C_{12}H_{13}Br$: C, 60·75; H, 5·55; Br, 33·7%), $\lambda_{max.}$ (95% ethanol) 223 (log ε 3·95), 252 (3·95), 279 (3·09), and 289 (2·95) mμ. The original procedure [8], in which pyridine is omitted, gave bis-[3-(inden-3-yl)propyl] ether in addition to the halide (52%; lit.,[8] 66%). In these experiments the reaction mixture was chromatographed on a column of alumina (neutral grade) first with n-hexane and then with benzene as eluant. The white residue from the final fractions gave the ether as prisms (2—3%), m.p. 77—78° [from ethanol–benzene (1 : 1)] (Found: C, 87·3; H, 7·7. Calc. for $C_{24}H_{26}O$: C, 87·25; H, 7·95%), $\lambda_{max.}$ (ethanol) 223 (log ε 4·21), 252 (4·27), 279 (3·16), and 289 (2·83) mμ, $\nu_{max.}$ (KBr) 1116 cm^{-1}. (C–O–C), τ (18% w/v solution in deuteriochloroform) 2·75 (8·2H, m, aromatic), 3·75 (2·1H, t, *J* 2 c./sec., vinyl protons), and 6·4—8·3 (16H, aliphatic).

Fluoren-1-amine (VII).—(*a*) 1-Aminofluoren-9-one (5·0 g., 26 mmoles) was dissolved in 85% hydrazine hydrate (15 ml.) and ethylene glycol (250 ml.) containing sodium hydroxide (9·0 g.). The water formed in the reaction was slowly distilled off during 24 hr. Addition of water (800 ml.) to the mixture precipitated the tan product, which was dissolved in hot ethanol (100 ml.). Water (100 ml.) was added to incipient cloudiness and the solution was cooled to yield the amine (VII) (4·1 g., 88%), m.p. 126° (lit.,[13] 124—125°), as tan prisms. A second crop (0·29 g., total yield 94%), m.p. 123—125°, was obtained by concentrating the mother liquor.

(*b*) A solution of the oxime (I) (132 mg., 0·714 mmole)

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[13] E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, 1953, **18**, 864.

in acetic acid (3·0 ml.) and acetic anhydride (1·9 ml., 20 mmoles) was heated on a steam-bath and hydrogen chloride was passed through for 2 hr. After removal of the solvent under reduced pressure the brown residue was dissolved in ethanol (4·0 ml.) and the solution was decolourized with Norit-A. Water was then added to the hot ethanolic solution to incipient cloudiness. Cooling caused deposition of the amide (VIII) as needles (52 mg., 35%), m.p. 194° (lit.,[13] 190—191°). Concentration of the mother liquor yielded a second crop (34 mg.), m.p. 191—193° (total yield 58%). In a large-scale run the oxime (I) (3·19 g.) was treated as above and the amide (VIII) (1·73 g.; m.p. 194—195°) crystallized from the reaction mixture when left at room temperature for 24 hr. More product (1·34 g.), m.p. 190—194°, was obtained on dilution of the mother liquor with water (total yield 86%). The amide (VIII) (250 mg.) was hydrolyzed when heated under reflux in 50% ethanolic hydrogen chloride for 1 hr. The solution was diluted with water and made alkaline with concentrated ammonium hydroxide to give a precipitate of the amine (VII) (180 mg., 90%), m.p. 123—125°, i.r. spectrum identical with that of the product of (*a*). The amide (VIII) was also obtained when the *O*-acetyl derivative of (I) was subjected to the rearrangement conditions described above. **3,4-*Dihydrofluoren*-1(2H)-*one* O-*acetyloxime*** (II) was prepared by heating a solution of the oxime (I) (0·71 g.) in acetic anhydride (10 ml.) and pyridine (0·20 ml.) on a steam-bath for 10 min. The mixture was poured into water and the precipitate (0·76 g., 86%), gave the *product* (II), m.p. 173—174° (from 95% ethanol) (Found: C, 75·0; H, 6·35; N, 5·75. $C_{15}H_{15}NO_2$ requires C, 74·65; H, 6·25; N, 5·8%), $\nu_{max.}$ (KBr) 1775 (C=O) and 1220 and 1225 (OAc) cm.$^{-1}$.

Isolation of Fluoren-1-*ol* (V) *in the Aromatization of the Oxime* (I).—A solution of the oxime (I) (382 mg., 1·9 mmole) in acetic acid (10·0 ml.) and acetic anhydride (0·30 ml., 3·2 mmoles) was saturated with hydrogen chloride for 1 hr. while the mixture was heated on a steam-bath. Portions were withdrawn at intervals of 5—10 min. and delivered into 3·6N-sodium hydroxide (5·0 ml.). Basic and neutral products were removed by extraction of the alkaline mixture with ether (2 × 10 ml.). The aqueous phase was then acidified with concentrated hydrochloric acid and extracted with ether. The ether was evaporated off and the residue was dissolved in methanol and subjected to t.l.c. on silica gel GF_{254} (20 × 20 cm.; 0·5 mm. thick) with chloroform–methanol (99 : 1). The isolated compound appeared as a single, fluorescence-quenching spot on exposure of the chromatograms to u.v. light (2537 Å), R_F value (0·36) identical with that of authentic (V). The silica gel containing the compound was extracted with methanol (2 × 2·0 ml.) and the solvent was evaporated off. The residue was rechromatographed on silica gel GF_{254} with benzene–ethyl acetate (1 : 1); R_F value (0·69) again closely similar to that of authentic (V) (0·71). The rechromatographed compound was extracted with methanol as above. The u.v. absorption spectra of the extract matched the spectrum of authentic (V). A plot of the concentration of (V) against time (Figure) showed a maximum 10—15 min. after the start of the reaction and declined thereafter. The methanolic solutions containing the rechromatographed (V) were combined and the solvent was evaporated off. The residue, dissolved in 1·2N-sodium hydroxide (4·0 ml.), was treated with benzoyl chloride (0·008 ml.). The mixture was extracted with ether (2 × 25 ml.) and the ether was washed with water (10 ml.). The ether was evaporated off and the residue was dissolved in methanol; portions (0·5 ml.) were chromatographed on silica gel GF_{254} with chloroform–acetone (95 : 5); this separated the benzoate of (V) (R_F 0·75) from a slow-moving impurity (R_F 0·37). The benzoate was extracted from the gel with methanol and rechromatographed on silica gel GF_{254} with cyclohexane–ethyl acetate (8 : 2). The mobility of the purified derivative in this solvent was identical with that of an authentic sample of the benzoate of (V) (R_F 0·49). The u.v. absorption spectrum of the twice chromatographed compound likewise matched that of the authentic benzoate of (V). **1-*Benzoyloxyfluorene***, prepared (249 mg., 51%) by treating fluoren-1-ol (V) (310 mg., 1·7 mmole) in 1·2N-sodium hydroxide (10 ml.) with benzoyl chloride (0·25 ml. 2·2 mmoles), had m.p. 122—123° (from 95% ethanol) (Found: C, 83·7; H, 4·95. $C_{20}H_{14}O_2$ requires C, 83·9; H, 4·95%), $\nu_{max.}$ (KBr) 1730 cm.$^{-1}$ (C=O), $\lambda_{max.}$ (MeOH) 218infl., 235 (log ε 4·11), 253 (4·15), 258 (4·18), 263 (4·38), 285 (3·66), and 297 (3·67) mμ.

TABLE 1

R_F Values [a] of isomeric fluorenylhydroxamic acids and of the corresponding amides (Whatmann 3MM paper)

	$R_F \times 100$ System (1) [b]	$R_F \times 100$ System (2) [c]
N-Fluoren-1-ylacetamide	51—62 [d]	69 [e]
N-Fluoren-1-ylacetohydroxamic acid	64—68 [f]	71 [g]
N-Fluoren-2-ylacetamide	52—62 [d]	63 [d]
N-Fluoren-2-ylacetohydroxamic acid	65—71 [f]	68 [g]
N-Fluoren-3-ylacetamide	51—62 [e]	66 [a]
N-Fluoren-3-ylacetohydroxamic acid	61—69 [f]	71 [g]
N-Fluoren-4-ylacetamide	34—47 [d]	67 [d]
N-Fluoren-4-ylacetohydroxamic acid	49—58 [e, f]	70 [g]

[a] For *ca.* 30 μg. of material. [b] Cyclohexane–t-butyl alcohol–pyridine–water (16 : 2 : 2 : 1). [c] Cyclohexane–t-butyl alcohol–acetic acid–water (16 : 4 : 2 : 1). [d] Quenches under u.v. light (2537 Å). [e] Fluoresces under u.v. light 2537 Å). [f] Yellow spot in daylight. [g] Brown spot in daylight.

Determination of the Formation of Amine (VII) *and Amide* (VIII) *in the Aromatization of Oxime* (I).—In a parallel experiment, under the same conditions as described for the isolation of (V), the quantities of amine (VII) and amide (VIII) formed in the rearrangement of oxime (I) were estimated on portions withdrawn from the reaction mixture at stated intervals and delivered into 3·6N-sodium hydroxide. Each alkaline solution was extracted with ether (2 × 25 ml.) and the ether was washed with water (10 ml.). The ether was then evaporated off and the residue was dissolved in methanol (25·0 ml.). Portions of this solution were applied to silica gel GF_{254} and the chromatograms were developed twice with chloroform–methanol (199 : 1). The amine (VII) (R_F 0·71) was cleanly separated from the oxime (I) (R_F 0·43) and from several unknown minor components. After extraction of the amine (VII) from the gel with methanol (2 × 2·0 ml.) the amounts of (VII) in the methanolic solution were determined spectrophotometrically and the molarity of (VII) in the reaction mixture was calculated. The u.v. spectrum of the isolated product was identical with that of authentic amine (VII) [13]: $\lambda_{max.}$ (MeOH) 250 (log ε 4·26), 260infl, 264, 285infl, and 293 mμ. T.l.c. in the above solvent system was not sufficient to give pure amide (VIII). The compound [R_F in chloroform–methanol (199 : 1) 0·33] was extracted from the gel with methanol

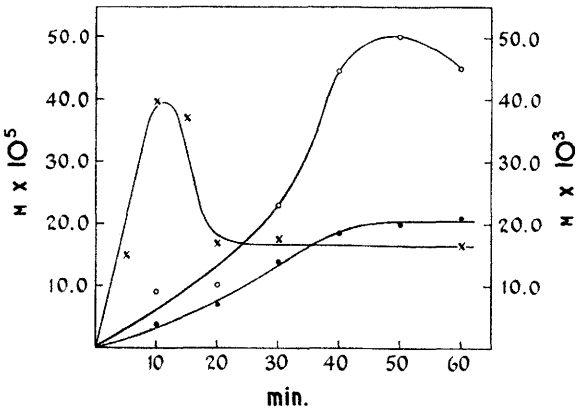
and rechromatographed on silica gel GF_{254} with benzene–ethyl acetate (1 : 1) to separate the amide (VIII) (R_F 0·29) from two unknown contaminants (R_F 0·50 and 0·72). The u.v. spectrum of the isolated amide (VIII) was now identical with that of authentic (VIII): $\lambda_{max.}$ (MeOH) 250 (log ε 4·29), 257infl, 263, 287infl, and 299 mμ. The molarity of (VIII) was calculated as described for (VII). Corrections were made for losses of (VII) and (VIII) during isolation and purification. A plot of the molarities of (VII) and (VIII) against time (Figure) indicated that the amounts of (VII) and (VIII) formed in the reaction approached limiting values. Under the experimental conditions (VII) accounted for 67% and (VIII) for 33% of the isolated products of the aromatization of (I) (Table 2).

TABLE 2

Relative amounts of fluoren-1-amine (A) and *N*-fluoren-1-ylacetamide (B) formed in the aromatization of 3,4-dihydrofluoren-1(2H)-one oxime *

Time (min.)	Molarity of (A)	Molarity of (B)	[Mole fraction of (A)] × 100
10	$9·22 \times 10^{-3}$	$4·22 \times 10^{-3}$	68·6
20	$1·02 \times 10^{-2}$	$7·10 \times 10^{-3}$	59·0
30	$2·35 \times 10^{-2}$	$1·45 \times 10^{-2}$	61·8
40	$4·47 \times 10^{-2}$	$1·85 \times 10^{-2}$	70·7
50	$5·04 \times 10^{-2}$	$2·00 \times 10^{-2}$	71·6
60	$4·49 \times 10^{-2}$	$2·11 \times 10^{-2}$	68·0

* Molar ratio of oxime to acetic anhydride 1 : 1·6.



The concentrations of fluoren-1-ol (M × 10^5) (×——×), fluoren-1-amine (M × 10^3) (○——○), and *N*-fluoren-1-ylacetamide (M × 10^3) (●——●) at various times during the aromatization of the oxime of 3,4-dihydrofluoren-1(2*H*)-one; molar ratio of oxime to acetic anhydride 1 : 1·6; each value is the average of duplicate determinations

1-*Nitrofluorene*.—A solution of maleic anhydride (16·0 g., 0·163 mole) in methylene chloride (800 ml.) was cooled to 0°. Hydrogen peroxide (90%, 63N by titration; 9·42 ml., 0·296 mole) was added and the mixture was kept at 0° for 2 days. It was then warmed slowly and, as soon as boiling commenced, the amine (VII) (4·0 g., 0·022 mole) in methylene chloride (30 ml.) was added dropwise to the vigorously stirred mixture during 5 min. The mixture was heated under reflux for a further 0·5 hr. and the tan precipitate was processed as described below. The filtrate was washed with water, 2N-sodium hydroxide, and water and dried ($MgSO_4$), and the solvent was evaporated off. The solid residue was chromatographed on a column of alumina (neutral grade) and eluted with n-hexane–methylene chloride (4 : 1). 1-Nitrofluorene was obtained from the first yellow band to emerge. The compound (2·84 g., 61%) gave yellow *needles*, m.p. 104—106° (from n-hexane–methylene chloride) (Found: C, 73·95; H, 4·5; N, 6·6. $C_{13}H_9NO_2$ requires C, 73·9; H, 4·3; N, 6·65%), $\lambda_{max.}$ (95% ethanol) 260 (log ε 4·43), 270infl (4·30), 288infl (3·81), and 333 (3·51) mμ, $\nu_{max.}$ (KBr) 1342 and 1523 $cm.^{-1}$ (NO_2).* The tan precipitate (see above) was suspended in water (500 ml.) and stirred for 3 hr. The water-insoluble material was dissolved in hot ethanol and water was added to incipient cloudiness. N-*Fluoren*-1-*ylmaleamicacid* gave brown needles (0·15 g., 8%), m.p. 180—183° (Found: C, 72·8; H, 4·9; N, 5·3. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·7; N, 5·0%), $\lambda_{max.}$ (ethanol) 246infl (log ε 4·18), 257infl (4·31), 264 (4·36), 275infl (4·23), 283infl (4·05), and 299infl (3·92) mμ, $\nu_{max.}$ (KBr) 3400 (OH), 3340 (NH), and 1715 and 1630 (C=O) $cm.^{-1}$. In another oxidation the molar ratio of (VII) to maleic anhydride and hydrogen peroxide was 1 : 3 : 5; the product was chromatographed in n-hexane containing increasing amounts of benzene. Under these conditions a second yellow band was eluted. Partial evaporation of the eluate gave 1,1′-*azoxyfluorene* as yellow needles (0·149 g., 6%), m.p. 235—238° (Found: C, 83·45; H, 4·6; N, 7·25. $C_{26}H_{18}N_2O$ requires C, 83·4; H, 4·85; N, 7·5%), $\lambda_{max.}$ (95% ethanol) 264 (log ε 4·50), 268 (4·51), 272infl (4·48), 290 (4·10), and 326 (4·21) mμ.

N-*Fluoren*-1-*ylacetohydroxamic Acid*.— 1-Nitrofluorene (2·00 g., 9·50 mmoles) in ethyl acetate (100 ml.), triethylamine (0·17 ml.), and acetic anhydride (3·3 ml., 35 mmoles) was hydrogenated over 10% palladium–charcoal (0·20 g.) at atmospheric pressure and room temperature until hydrogen (20 mmoles) had been consumed. The catalyst was filtered off and the solution was stirred at room temperature overnight with 8M-ammonium hydroxide (30 ml.). The organic phase was extracted with 5% sodium hydroxide (8 × 8 ml.). The product, which settled as an oil upon acidification of the basic extract with concentrated hydrochloric acid, solidified when the mixture was stirred at 0° for 15 min. The crude product was dissolved in hot ethanol (7 ml.) and the solution was brought to incipient cloudiness with water. N-*Fluoren*-1-*ylacetohydroxamic acid* crystallized as flakes (0·66 g., 29%), m.p. 70—80° (Found: C, 75·0; H, 5·35; N, 5·95. $C_{15}H_{13}NO_2$ requires C, 75·3; H, 5·5; N, 5·85), $\lambda_{max.}$ (ethanol) 257 (log ε 4·30), 262 (4·30), 273infl (4·11), 291 (3·69), 295infl (3·66), and 303 (3·80) mμ; $\nu_{max.}$ (KBr) 3350 and 2900 (broad, OH) and 1630 (C=O) $cm.^{-1}$. The solvent of the organic phase was evaporated off and the residue was chromatographed on a column of alumina (neutral grade, 30 g.) in n-hexane, with 25% methylene chloride–n-hexane as eluant. The proportion of methylene chloride in the eluant was gradually increased. The first fractions yielded 1-nitrofluorene (10%) and the final fractions gave amide (VIII) (25%) identified by i.r. spectrum and m.p. N-*Acetoxy*-N-*fluoren*-1-*ylacetamide* was prepared by dissolving the hydroxamic acid (1·0 g., 4·2 mmoles) in a slight excess of 0·1N-sodium hydroxide and adding acetic anhydride (1·2 ml., 12 mmoles). The oily precipitate was dissolved in benzene and the solution was dried ($MgSO_4$). It was then concentrated to 3 ml. and n-heptane (10 ml.) was added, whereupon the product settled as an

* The method of White and Emmons [4] was first applied to the oxidation of fluoren-1-amine by Burtle and Morath, who obtained a compound m.p. 105—106·5° with u.v. absorption similar to that reported here (J. G. Burtle, personal communication).

oil (60%) (Found: C, 72·85; H, 5·6; N, 5·05. $C_{17}H_{15}NO_3$ requires C, 72·6; H, 5·35; N, 5·0%). The mother liquor was cooled at 4° for 5 days and yielded the product as yellow prisms (4%), m.p. 55—60° (Found: C, 72·6; H, 5·3; N, 4·8%), $\lambda_{max.}$ (95% ethanol) 250infl (log ε 4·06), 254infl (4·16), 259infl (4·19), 263 (4·22), 273infl (4·06), 294 (3·76), and 303 (3·83) mμ, $\nu_{max.}$ (KBr) 1798 and 1690 cm.$^{-1}$, $\nu_{max.}$ (film) 1795 and 1690 cm.$^{-1}$ (C=O).

A better method of acetylation is to dissolve the hydroxamic acid in pyridine, to add acetic anhydride, and to precipitate the product with cold water.

Fluoren-3-amine.—A mixture of 3-nitrofluoren-9-one (15·0 g., 67 mmoles), hydrazine hydrate (95%; 24·0 ml.), and potassium hydroxide (26·0 g.) in ethylene glycol (600 ml.) was heated below the b.p. for 6 hr. It was then heated under reflux for 10 hr.; the water formed in the reaction (30 ml.) was distilled off. The product was precipitated with water (2·5 l.) and purified by addition of water to a solution in hot ethanol (600 ml.) to cloudiness. Fluoren-3-amine (7·74 g., 64%), m.p. 145—150° (lit.,[3] 152—153°), separated as a tan powder. A second crop (1·56 g., total yield 77%) was obtained from the mother liquor.

3-*Nitrofluorene*.—To an oxidation mixture prepared by the addition of hydrogen peroxide (90%, 73N by titration; 1·73 ml., 0·0625 mole) to maleic anhydride (2·45 g., 0·0250 mole) in methylene chloride (175 ml.) as described for the oxidation of fluoren-1-amine, was added fluoren-3-amine (1·00 g., 5·33 mmoles) in methylene chloride during 5 min. The solution was heated under reflux for 0·5 hr. and 3-nitrofluorene (0·59 g., 51%), m.p. 103—106° (lit.,[14] 105°), was isolated and purified by chromatography on alumina as described for 1-nitrofluorene. 3-Nitrofluoren-9-one (3%), identified by m.p. and i.r. spectrum, was obtained from the last band emerging from the column.

3′-*Nitrospiro*[1,3-*dithiolan*-2,9′-*fluorene*].—To a solution of 3-nitrofluoren-9-one (2·4 g., 0·101 mole) in chloroform (250 ml.) was added ethanedithiol (10 ml.) and hydrogen chloride was passed through for 16 hr. The mixture was washed with dilute sodium hydrogen carbonate solution and dried ($MgSO_4$). The solvent was evaporated off under reduced pressure to leave a reddish *solid* (3·1 g., 98%), m.p. 225° (Found: C, 59·85; H, 3·95; N, 4·3. $C_{15}H_{11}NO_2S_2$ requires C, 59·8; H, 3·7; N, 4·65%), $\lambda_{max.}$ (ethanol) 261 (log ε 4·24), 285infl (4·06), and 300infl (3·34) mμ, $\nu_{max.}$ (KBr) 1528 and 1340 cm.$^{-1}$ (NO_2). Desulphurisation of the spiro-compound with Raney nickel [15] gave 3-nitrofluorene (14%), m.p. 98—100°, i.r. spectrum identical with that of 3-nitrofluorene obtained by oxidizing fluoren-3-amine with peroxymaleic acid.

N-*Fluoren-3-ylacetohydroxamic Acid*.—To 3-nitrofluorene (3·00 g., 14·2 mmoles) in freshly distilled ethyl acetate (800 ml.) were added acetic anhydride (3·5 ml., 36 mmoles) and triethylamine (3·5 ml.). The mixture was hydrogenated over 10% palladium–charcoal (0·50 g.) at atmospheric pressure and room temperature until hydrogen (28·4 mmoles) had been consumed. The hydroxamic acid was isolated as described for the 1-isomer. After two crystallizations from ethanol–water the *product* (0·90 g., 27%), m.p. 132—134°, was obtained as prisms (Found: C, 75·15; H, 5·7; N, 5·6. $C_{15}H_{13}NO_2$ requires C, 75·3; H, 5·5; N, 5·85%), $\lambda_{max.}$ (ethanol) 252 (log ε 4·46), 302 (3·80), and 313 (3·71) mμ, $\nu_{max.}$ (KBr) 3120 and 2900 (broad, OH) and 1610 (C=O) cm.$^{-1}$. The ethyl acetate was evaporated off and the residue was chromatographed on alumina (neutral grade) as described for the 1-isomer, with benzene–n-hexane (1 : 1) followed by benzene containing increasing amounts of ethyl acetate as eluant. The first fractions yielded 3-nitrofluorene (22%). N-Fluoren-3-ylacetamide (21%), m.p. 193—194° (lit.,[13] 189—190°), was obtained from the final fractions eluted with benzene–ethyl acetate.

Fluoren-4-amine.—A solution of 4-aminofluoren-9-one (8·0 g., 41 mmoles) and 85% hydrazine hydrate (24 ml.) in ethylene glycol (250 ml.) containing sodium hydroxide (1·0 g.) was heated under reflux for 5 hr.; the water formed was distilled off. Addition of water (1·5 l.) to the mixture precipitated fluoren-4-amine (7·3 g., 98%), m.p. 115° (lit.,[16] 115—116°).

4-*Nitrosofluorene*.—A solution of maleic anhydride (7·50 g., 77 mmoles) in methylene chloride (190 ml.) was cooled to 0° and hydrogen peroxide (90%, 63N by titration; 7·50 ml., 0·472 mole) was added. The mixture was stirred at 0° for 1 hr. and then left at 0° for 2 days. Fluoren-4-amine (2·0 g., 11 mmoles) in methylene chloride (25 ml.) was then added in one portion. The mixture was stirred at 0° for 1 hr., then washed with water, 0·5N-sodium hydroxide, and water. The organic phase was dried ($MgSO_4$) and the solvent was evaporated off. The residue was chromatographed on alumina (neutral grade) with n-hexane containing increasing amounts of methylene chloride as eluant. The product was obtained as green *needles* from the first yellow band to emerge (0·70 g., 32%). A second crop (0·24 g.), obtained from the mother liquor, had m.p. 111—112° (from methylene chloride–n-hexane) (Found: C, 80·2; H, 4·7; N, 7·0. $C_{13}H_9NO$ requires C, 80·0; H, 4·65; N, 7·15%), $\lambda_{max.}$ (95% ethanol) 240infl (log ε 4·14), 256 (4·30), 301 (3·68), 326 (3·79), and 400 (3·74) mμ, $\nu_{max.}$ (KBr) 1490 and 1460 cm.$^{-1}$ (N=O).

4-*Nitrofluorene*.—Fluoren-4-amine (7·0 g., 0·039 mole) in methylene chloride was added in one portion to a mixture of hydrogen peroxide (90%, 63N by titration; 22·0 ml., 0·693 mole) and maleic anhydride (28·0 g., 0·287 mole) in methylene chloride (700 ml.), prepared as for the oxidation of fluoren-1- and 3-amines. The mixture was heated under reflux for 1 hr. and the product was isolated and purified as described for the 1- and 3-isomers. 4-Nitrofluorene (4·22 g., 52%), m.p. 74—75° (lit.,[16] 75—76°) gave yellow needles. Extraction of the reaction mixture with aqueous base yielded 4-aminofluoren-9-one, which slowly precipitated from the basic solution and was identified by its i.r. spectrum and m.p.

N-*Fluoren-4-ylacetohydroxamic Acid*.— 4-Nitrofluorene (1·00 g., 4·74 mmoles) in ethyl acetate (80 ml.), acetyl chloride (1·3 ml., 18 mmoles), and triethylamine (0·15 ml.) was hydrogenated over 10% palladium–charcoal (0·15 g.) at room temperature and atmospheric pressure until hydrogen (9·48 mmoles) had been consumed. The hydroxamic acid was isolated as described for the 1- and 3-isomers. The crude product gave N-(*fluoren-4-yl*)*acetohydroxamic acid* (30 mg., 2·6%), m.p. 147—153° (from ethanol–water), as white flakes (Found: C, 75·05; H, 5·55; N, 5·7. $C_{15}H_{13}NO_2$ requires C, 75·3; H, 5·5; N, 5·85%), $\lambda_{max.}$ (ethanol) 251infl (log ε 4·07), 263infl (4·10), 266 (4·11), 290 (3·85), and 301 (3·78) mμ, $\nu_{max.}$ (KBr) 3250 (sharp, OH) and 1640 (C=O) cm.$^{-1}$.

The 8M ammonium hydroxide solution which had been

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[15] G. Stork and J. W. Schulenberg, *J. Amer. Chem. Soc.*, 1962, **84**, 284.
[16] J. H. Weisburger, E. K. Weisburger, and H. P. Morris, *J. Amer. Chem. Soc.*, 1952, **74**, 4540.

used in the hydrolysis of the *N*-acetoxy-*N*-fluoren-4-ylacetamide to the hydroxamic acid was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (2 × 10 ml.). The ethyl acetate was evaporated off and the oily residue was dissolved in ethanol (4 ml.). Dilution with water yielded *N*-(fluoren-4-yl)acetohydroxamic acid (17 mg., 1·5%), m.p. 146—152°. The mixture which had been extracted with base was chromatographed on a column of alumina (neutral grade). 4-Nitrofluorene (24%) was eluted with benzene, and *N*-fluoren-4-ylacetamide (24%), m.p. 203—204° (lit.,[16] 199—200°), was obtained from the final fractions brought off with benzene containing increasing amounts of ethyl acetate.

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