

6(5*H*)-Phenanthridinones. II. Preparation of Substituted 6(5*H*)-Phenanthridinones from 9-Oxofluorenes (1,2)

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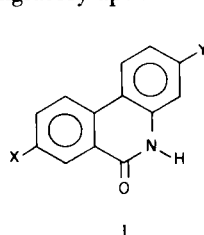
A number of 6(5*H*)-phenanthridinones have been conveniently prepared from 9-oxofluorenes through the Schmidt reaction. It has been found that all amino and nitro 9-oxofluorenes thus far tried gave substituted 6(5*H*)-phenanthridinones with the amino or nitro group situated in the benzene ring attached to the nitrogen of the lactam group. UV and IR spectral data are presented for these compounds.

We recently showed (2) that 3,8-disubstituted 6(5*H*)-phenanthridinones, with the substituents identical, can be readily prepared from the corresponding 9-oxofluorene oximes in the Beckmann rearrangement reaction. Certain mono- and disubstituted 6(5*H*)-phenanthridinones, which cannot be conveniently prepared in this way because of formation of two difficultly separable isomers, can be readily obtained from the corresponding 9-oxofluorenes through a Schmidt reaction [see Table I and (3a,b)]. This rearrangement gives a principal product with a nitro or amino group situated in the benzene ring connected to the nitrogen of the lactam linkage. Thus, 2-nitro-9-oxofluorene yields 3-nitro-6(5*H*)-phenanthridinone (4) and 1-amino-9-oxofluorene gives high yields of 4-amino-6(5*H*)-phenanthridinone (2); 4-amino-9-oxofluorene and 4-nitro-9-oxofluorene are rearranged under these conditions to 1-amino- and 1-nitro-6(5*H*)-phenanthridinones (IIIa,b) respectively. Likewise, 3-chloro- and 8-chloro-2-nitro-6(5*H*)-phenanthridinones (IIIh and IIi) are recovered from the rearrangements of 2-chloro- and 7-chloro-3-nitro-9-oxofluorenes.

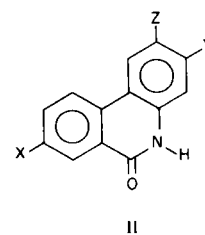
In general, strongly electron-withdrawing substituents, e.g., nitro and amino (the latter as -NH_3^+), promote fission of the bond between the 9-carbon atom of the fluorenone and the ring bearing that substituent; this ring migrates in high yield to nitrogen, thus completing the lactam linkage. The carboxyl group has been found to have the same effect (5).

When there are electron-donating groups (methoxyl for example) on the fluorenone nucleus, more or less equal quantities of the two possible isomers are obtained from the Schmidt reaction. The above facts are as true when the substituents (nitro, methoxy, etc.) are in the *para* position to the carbonyl of the fluorenone (where the groups offer no steric hindrance) as they are when the groups are in any other position. No one seems to have

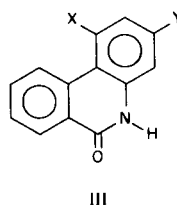
offered a clear explanation of this (6). Gould (3b) for unsymmetric ketones, "would expect the bulkier of the two groups in the parent ketone to migrate preferentially" but "unsymmetrically *para*-substituted benzophenones generally give nearly equal quantities of both amides, for . . . steric effects are negligible." Electronic effects would therefore seem to play a major part in this reaction for this group of compounds. We feel this to be the case in spite of "recent evidence [cited in footnote (20), reference 3b] that electronic effects play little part in determining migratory aptitudes in the Schmidt reaction."



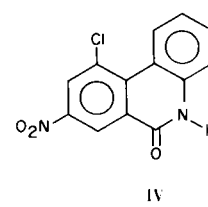
	X	Y
a,	Br	NH ₂
b,	Br	NO ₂
c,	Cl	NH ₂
d,	Cl	NO ₂
e,	Br	H
f,	Cl	H



	X	Y	Z
a,	Br	Br	NO ₂
b,	Cl	Cl	NO ₂
c,	Br	Br	NH ₂
d,	Cl	Cl	NH ₂
e,	Cl	NH ₂	NO ₂
f,	Cl	H	NO ₂
g,	Cl	H	NH ₂
h,	H	Cl	NO ₂

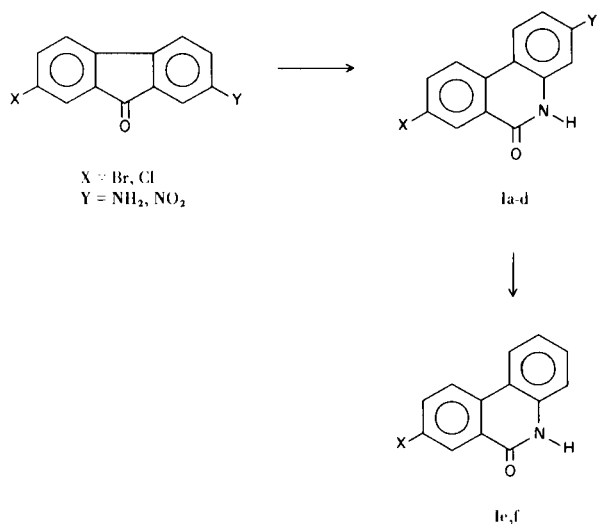


	X	Y
a,	NH ₂	H
b,	NO ₂	H
c,	Cl	NO ₂



Utilizing this seemingly electronic effect we have prepared 8-halogeno derivatives (Ia-d) of 3-amino- and 3-nitro-6(5*H*)-phenanthridinones from the corresponding 7-halogeno derivatives of 2-amino and 2-nitro-9-oxofluorenes. The products were deaminated giving 8-halogeno phenanthridinones (Ie,f) (Scheme I). A Beckmann rearrangement of 2-nitro-7-chloro-9-oxofluorene oxime in polyphosphoric acid surprisingly gave 8-chloro-3-nitro-6(5*H*)-phenanthridinone (Id), in good yields, as the only detectable product.

SCHEME I



Nitration of 8-chloro-6(5*H*)-phenanthridinone (If) gave the 2-nitro derivative (IIe). This compound was also prepared by the rearrangement of 7-chloro-3-nitro-9-oxofluor-

ene or of 2-amino-7-chloro-3-nitro-9-oxofluorene followed by deamination of the rearrangement product (IIe) (Scheme II). Reduction of IIe with Raney nickel and hydrazine hydrate (7) in 95% ethanol gave 2-amino-8-chloro-6(5*H*)-phenanthridinone (IIg).

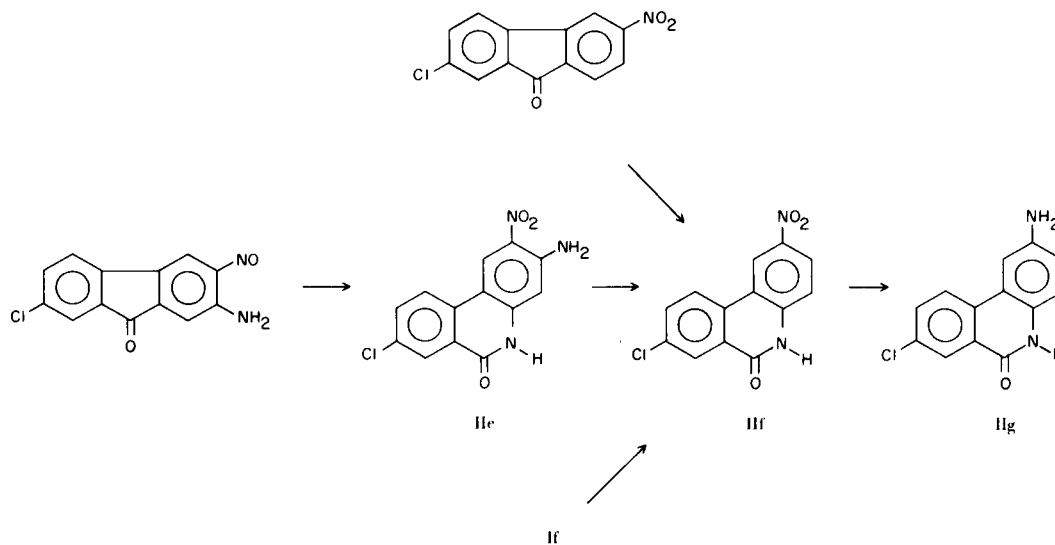
Likewise, rearrangement of 2-chloro-3-nitro-9-oxofluorene gave predominantly 3-chloro-2-nitro-6(5*H*)-phenanthridinone (IIh) rather than the 8-chloro-9-nitro isomer. The structure of IIh was substantiated by nitration of 3-chloro-6(5*H*)-phenanthridinone and by reduction-dechlorination to the known 2-aminophenanthridinone with palladium-on-carbon and hydrazine hydrate (7) in refluxing 95% ethanol (Scheme III).

This reduction-dehalogenation procedure was also employed in the elucidation of the structure of the nitrated 3,8-dihalogonphenanthridinones (IIa,b) (Scheme IV). In each case 2-amino-6(5*H*)-phenanthridinone was obtained indicating that the 2-position of these substituted phenanthridinones had been nitrated as in the case with 6(5*H*)-phenanthridinone itself (8).

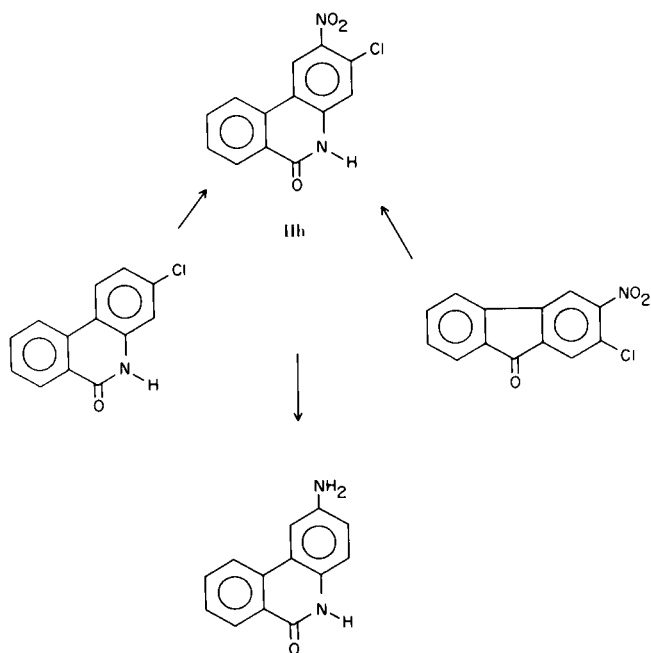
Rearrangement of 4-chloro-2-nitro-9-oxofluorene gave a 1,3-substituted phenanthridinone (IIIc). The other possible product, namely 10-chloro-8-nitro-6(5*H*)-phenanthridinone (IV), was synthesized by coupling methyl 2-bromobenzoate and 3-chloro-4-iodonitrobenzene followed by hydrolysis of the ester to 2-(2'-chloro-4'-nitrophenyl)benzoic acid. The latter was converted to 2-(2'-chloro-4'-nitrophenyl)aniline, which gave the isocyanate with phosgene. Subsequent cyclization gave IV (Scheme V).

The ultraviolet absorptions of these 6(5*H*)-phenanthridinones were determined in absolute ethanol and the data are presented in Table II. In general, these spectra are

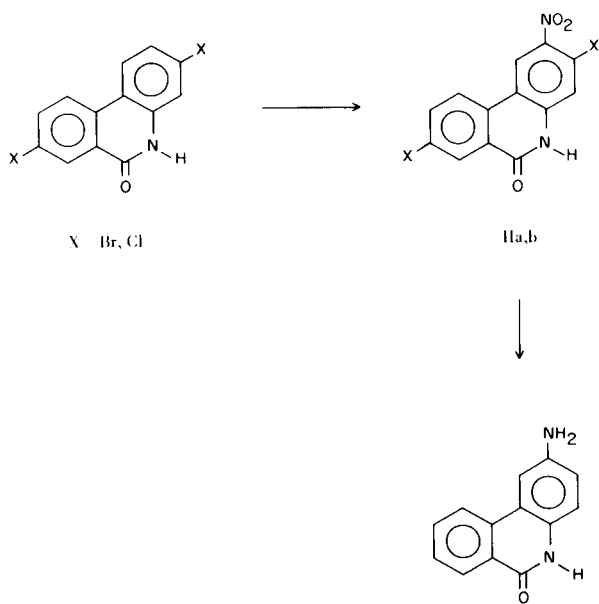
SCHEME II



SCHEME III



SCHEME IV



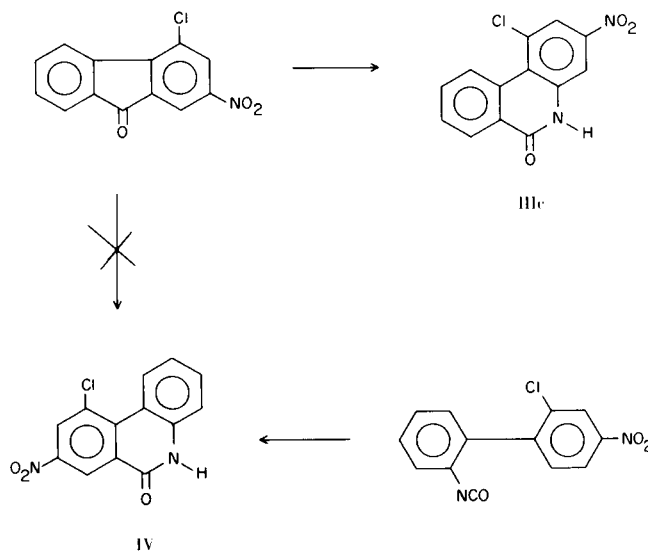
complex, a notable exception being that of 10-chloro-8-nitrophenanthridinone which has only one maximum (251 $m\mu$).

The infrared absorptions of the phenanthridinones lie in the expected ranges. Absorption bands assigned to —C—NH (lactam) (two), C=O (fluorenones), NO_2 , 2

adjacent H's, and 4 adjacent H's are noted in the experimental section.

These compounds have been submitted for both anti-tumor and antimalarial screening and the biological data will be reported later.

SCHEME V



EXPERIMENTAL

Melting points below 250° were taken on a Fisher-Johns block and are corrected to standards. Melting points above 250° were taken with a Hoover capillary melting point apparatus and are uncorrected. Analyses were performed by A. Bernhardt, Elbach über Engelskirchen, West Germany. The ultraviolet absorption spectra were run on a Beckman DK-1 recording spectrophotometer (in absolute ethanol) and the infrared spectra were made with potassium bromide disks on a Beckman IR-5.

3-Amino-8-bromo-6(5*H*)-phenanthridinone (1a).

(a) From 2-Amino-7-bromo-9-oxofluorene.

A mixture of 2-amino-7-bromo-9-oxofluorene (9) (5.5 g., 0.02 mole) and concentrated sulfuric acid (150 ml.) was chilled in ice while, with stirring, a saturated aqueous solution of sodium azide (2.0 g., 0.03 mole) was added dropwise in 2 hours. After all the azide solution had been added the reaction mixture was continuously stirred first in the ice-bath for several hours and then at ambient temperature overnight. The solution was diluted with water (150 ml.) and the amine sulfate was treated with an excess of dilute sodium hydroxide. The product was separated and recrystallized from 95% ethanol giving shiny gray needles, 3.2 g. (55%); ir cm^{-1} , ν max (—CONH—) 3200, 1670; (two adjacent hydrogens) 805.

(b) From Reduction of Compound Ib.

8-Bromo-3-nitro-6(5*H*)-phenanthridinone (1b) (1.6 g., 5 mmoles) was mixed with stannous chloride dihydrate (10 g.) and concentrated hydrochloric acid (50 ml.). The mixture was boiled with constant stirring for 15 minutes, cooled and treated with 2*N* sodium hydroxide (250 ml.) giving 1.3 g. (90%) of the product.

TABLE I
Substituted 6(5*H*)-Phenanthridinones

Compound	Substituent(s)	M.p., °C	Formula	C	H	N	X
Ia	3-NH ₂ , 8-Br	341-343 dec	C ₁₃ H ₉ BrN ₂ O	54.00 (53.67)	3.14 (3.24)	9.69 (9.66)	27.64 (27.88) (a)
Ib	3-NO ₂ , 8-Br	335-336	C ₁₃ H ₇ BrN ₂ O ₃	48.93 (48.87)	2.21 (2.32)	8.78 (8.75)	25.04 (24.90) (a)
Ic	3-NH ₂ , 8-Cl	340-342 dec	C ₁₃ H ₉ ClN ₂ O	63.81 (63.94)	3.71 (3.83)	11.45 (11.45)	14.49 (14.31) (b)
Id	3-NO ₂ , 8-Cl	347-348 dec	C ₁₃ H ₇ ClN ₂ O ₃	56.85 (56.70)	2.57 (2.42)	10.20 (10.04)	
Ie	8-Br	294-295	C ₁₃ H ₈ BrNO	56.96 (56.74)	2.94 (3.16)	5.11 (4.91)	29.15 (28.92) (a)
If	8-Cl	257-258 dec	C ₁₃ H ₈ ClNO	67.99 (67.79)	3.51 (3.55)	6.10 (6.23)	15.44 (15.53) (b)
IIa	3,8-Br ₂ , 2-NO ₂	> 360	C ₁₃ H ₆ Br ₂ N ₂ O ₃	39.23 (39.29)	1.52 (1.72)	7.04 (6.96)	40.15 (40.10) (a)
IIb	3,8-Cl ₂ , 2-NO ₂	> 360	C ₁₃ H ₆ Cl ₂ N ₂ O ₃	50.51 (50.67)	1.95 (1.94)	9.05 (8.96)	
IIc	2-NH ₂ , 3,8-Br ₂	317-318 dec	C ₁₃ H ₈ Br ₂ N ₂ O	42.42 (42.54)	2.19 (2.34)	7.61 (7.46)	43.42 (43.32) (a)
IId	2-NH ₂ , 3,8-Cl ₂	324-325 dec	C ₁₃ H ₈ Cl ₂ N ₂ O	55.94 (56.06)	2.89 (2.95)	10.04 (9.94)	25.40 (25.35) (b)
IIe	3-NH ₂ , 8-Cl, 2-NO ₂	> 360	C ₁₃ H ₈ ClN ₃ O ₃	53.90 (53.78)	2.78 (2.71)	14.51 (14.38)	12.24 (12.14) (b)
IIf	8-Cl, 2-NO ₂	> 360	C ₁₃ H ₇ ClN ₂ O ₃	56.85 (56.84)	2.57 (2.82)	10.20 (10.29)	12.91 (13.03) (b)
IIg	8-Cl, 2-NH ₂	286-287 dec	C ₁₃ H ₉ ClN ₂ O	63.81 (64.08)	3.71 (4.08)	11.45 (11.17)	
IIh	3-Cl, 2-NO ₂	362-363 dec	C ₁₃ H ₇ ClN ₂ O ₃	56.85 (57.17)	2.57 (2.45)	10.20 (10.33)	
IIIa	1-NH ₂	293-294 dec (c)	C ₁₃ H ₁₀ N ₂ O			13.33 (13.22)	
IIIb	1-NO ₂	297-298 (d)	C ₁₃ H ₈ N ₂ O ₃	65.00 (65.14)	3.36 (3.49)	11.66 (11.51)	
IIIc	1-Cl, 3-NO ₂	338-339 dec	C ₁₃ H ₇ ClN ₂ O ₃	56.85 (56.93)	2.57 (2.35)	10.20 (10.06)	12.91 (12.79) (b)
IV	10-Cl, 8-NO ₂	143-144 (e)	C ₁₃ H ₇ ClN ₂ O ₃	56.85 (56.78)	2.57 (2.66)	10.20 (10.08)	12.91 (12.77) (b)

(a) X=Br. (b) X=Cl. (c) Lit. (5), m.p. 319-323°. (d) Lit. (5), m.p. 325-327°. (e) Glassy melt.

TABLE II

Ultraviolet Absorption Data of Substituted 6(5H)-Phenanthridinones (a)

No.	Position of Substituent						λ max., $m\mu$ (ϵ max)
	C ₁	C ₂	C ₃	C ₄	C ₈	C ₁₀	
(b)	H	H	H	H	H	H	230 (52,300), 237 (45,600), 249 (15,200), 258 (18,600), 309 (6,100), 322 (8,500), 337 (7,400)
Ia	H	H	NH ₂	H	Br	H	225 (45,500), 228 (c) (45,000), 275 (16,800), 329 (15,900)
Ib	H	H	NO ₂	H	Br	H	220 (48,700), 264 (17,900), 307 (15,800), 359 (11,600)
Ic	H	H	NH ₂	H	Cl	H	224 (43,900), 230 (c) (41,600), 272 (c) (15,400), 282 (16,100), 328 (16,500), 360 (c) (7,600)
Id	H	H	NO ₂	H	Cl	H	220 (40,200), 265 (14,800), 305 (11,900) 357 (10,100)
Ie	H	H	H	H	Br	H	226 (c) (45,200), 231 (48,400), 264 (25,100), 272 (c) (17,000), 314 (7,800), 329 (9,200), 344 (7,300)
If	H	H	H	H	Cl	H	225 (c) (46,400), 230 (51,300), 262 (22,100), 272 (c) (14,900), 314 (c) (7,700), 326 (9,100), 337 (7,900)
IIa	H	NO ₂	Br	H	Br	H	210 (c) (30,400), 230 (30,100), 271 (34,200), 308 (c) (10,700), 330 (10,400), 344 (11,100)
IIb	H	NO ₂	Cl	H	Cl	H	229 (32,900), 261 (c) (27,900), 268 (31,000), 306 (c) (9,400), 329 (9,700), 343 (10,400)
IIc	H	NH ₂	Br	H	Br	H	214 (37,600), 234 (39,900), 240 (40,300), 261 (29,000), 272 (c) (24,700), 332 (c) (5,600), 346 (7,300), 368 (8,300)
IId	H	NH ₂	Cl	H	Cl	H	212 (36,800), 232 (38,600), 238 (40,000), 258 (c) (28,100), 332 (c) (5,500), 348 (c) (7,200), 366 (8,000)
IIe	H	NO ₂	NH ₂	H	Cl	H	212 (42,200), 250 (18,600), 278 (34,400), 296 (38,100), 331 (c) (13,700), 424 (6,800)
IIf	H	NO ₂	H	H	Cl	H	224 (32,400), 254 (22,700), 310 (c) (10,800), 320 (c) (11,100), 333 (11,900), 345 (12,300)
IIg	H	NH ₂	H	H	Cl	H	230 (32,300), 237 (33,700), 246 (c) (29,300), 361 (6,700)
IIh	H	NO ₂	Cl	H	H	H	226 (35,800), 254 (28,000), 264 (29,900), 300 (c) (10,500), 324 (10,300), 338 (11,500)
IIIa	NH ₂	H	H	H	H	H	220 (26,800), 238 (32,600), 286 (12,200), 302 (c) (9,900), 338 (4,900)
IIIb	NO ₂	H	H	H	H	H	229 (59,200), 252 (c) (15,900), 324 (c) (6,000), 336 (6,200)
IIIc	Cl	H	NO ₂	H	H	H	221 (34,300), 240 (c) (24,200), 248 (c) (22,800), 263 (19,500), 272 (17,000), 300 (c) (12,500)
IV	H	H	H	H	NO ₂	Cl	251 (14,700)

(a) Determined in absolute ethanol. Two or three stock solutions of each compound were prepared separately. These data are the average figures of the two or three separate determinations of each sample. (b) In good agreement with C. B. Reese, *J. Chem. Soc.*, 895 (1958). (c) Shoulder.

A mixture of the product with the compound in (a) showed no depression of the melting point.

8-Bromo-3-nitro-6(5*H*)-phenanthridinone (1b).

To a stirred and cooled (ice) solution of 2-nitro-7-bromo-9-oxofluorene (10) (6.1 g., 0.02 mole) in concentrated sulfuric acid (500 ml.), sodium azide (3.3 g., 0.05 mole) in water (10 ml.) was added dropwise over a period of 3 hours. After completion of the addition of the azide solution the reaction mixture was stirred further in the ice bath for 4 hours and then the cooling bath was removed. Stirring was continued for 20 hours and the mixture was poured into water giving 6.4 g. (100%) of the product (needles from acetic acid); ir cm^{-1} , ν max (-CONH-) 3180, 1670; (NO_2) 1350; (two adjacent hydrogens) 813.

3-Amino-8-chloro-6(5*H*)-phenanthridinone (1c).

(a)

This compound was prepared from 2-amino-7-chloro-9-oxofluorene (9) (6.9 g., 0.03 mole), concentrated sulfuric acid (125 ml.), and sodium azide (3.3 g., 0.05 mole) with the procedure as described in (a) in the preparation of 1a. The crude product was recrystallized from 95% ethanol giving 4.5 g. (61%) of lustrous needles; ir cm^{-1} , ν max (-CONH-) 3200, 1670; (two adjacent hydrogens) 805.

(b)

Compound 1d (0.5 g.) was mixed thoroughly with stannous chloride dihydrate (5 g.) and concentrated hydrochloric acid (25 ml.). The mixture was refluxed with stirring for 0.5 hour, cooled, and treated with 2*N* sodium hydroxide (150 ml.). The solid was filtered off, washed with water and recrystallized twice from 95% ethanol giving 0.3 g. of the amine. No melting point depression was observed when this amine was mixed with the product obtained in (a).

8-Chloro-3-nitro-6(5*H*)-phenanthridinone (1d).

(a) From 2-Nitro-7-chloro-9-oxofluorene.

2-Nitro-7-chloro-9-oxofluorene (11) (7.8 g., 0.03 mole), concentrated sulfuric acid (1000 ml.) and saturated aqueous sodium azide (2.1 g., 0.033 mole) solution were reacted as described previously. The product was recrystallized from acetic acid giving 6.6 g. (80%) of greenish crystals, and was found to be identical with the compound prepared in a Beckmann reaction as described below.

(b) From 2-Nitro-7-chloro-9-oxofluorene Oxime.

The oxime (2) (3 g., 0.011 mole) was mixed with polyphosphoric acid (150 g.). The mixture was heated with stirring at 190-195° for 15 minutes, cooled and triturated with water. The solid was collected on a filter, washed well with hot water and recrystallized from acetic acid giving 2.6 g. (87%) of the product; ir cm^{-1} , ν max (-CONH-) 3180, 1670; (NO_2) 1350; (two adjacent hydrogens) 815.

8-Bromo-6(5*H*)-phenanthridinone (1e).

3-Amino-8-bromo-6(5*H*)-phenanthridinone (1a) (0.9 g., 3 mmoles) was diazotized at 5-10° in a mixture of concentrated hydrochloric acid (30 ml.) and water (10 ml.) with a saturated aqueous solution of sodium nitrite (0.3 g., 4 mmoles). After stirring at 0-5° for 2 hours, cold 50% hypophosphorous acid (10 ml.) was added and the reaction mixture was continuously stirred at ambient temperature for 20 hours and then diluted with water. The product was separated and recrystallized from 95% ethanol

giving shiny platelets, 0.6 g. (74%); ir cm^{-1} , ν max (-CONH-) 3200, 1670; (two adjacent hydrogens) 818; (four adjacent hydrogens) 770.

8-Chloro-6(5*H*)-phenanthridinone (1f).

As in the preceding paragraph, 3-amino-8-chloro-6(5*H*)-phenanthridinone (1c) (2.5 g., 0.01 mole) was diazotized in 27% hydrochloric acid (100 ml.) with sodium nitrite (0.8 g., 0.011 mole) and the diazotization mixture was treated with 50% hypophosphorous acid (25 ml.) (16 hours) giving 2.3 g. (100%) of yellow crystals (ethanol); ir cm^{-1} , ν max (-CONH-) 3150, 1650; (two adjacent hydrogens) 825; (four adjacent hydrogens) 767.

3,8-Dibromo-2-nitro-6(5*H*)-phenanthridinone (IIa).

3,8-Dibromo-6(5*H*)-phenanthridinone (2) (10 g., 0.028 mole) was added in one portion to a stirred mixture of acetic acid (150 ml.) and 90% nitric acid (150 ml.). The mixture was stirred at 65-70° for 10 minutes and cooled. The prisms were collected, washed first with acetic acid followed by water and dried giving 8.7 g. (79%). Recrystallization from acetic acid gave small white needles; ir cm^{-1} , ν max (-CONH-) 3220, 1660; (NO_2) 1330; (two adjacent hydrogens) 825.

3,8-Dichloro-2-nitro-6(5*H*)-phenanthridinone (IIb).

A mixture of 3,8-dichloro-6(5*H*)-phenanthridinone (2) (22.7 g., 0.086 mole), acetic acid (250 ml.) and 90% nitric acid (250 ml.) was reacted the same way as described above giving 24.5 g. (92%) of the nitro compound. Recrystallization from acetic acid gave small white crystals; ir cm^{-1} , ν max (-CONH-) 3150, 1670; (NO_2) 1330; (two adjacent hydrogens) 833.

2-Amino-3,8-dibromo-6(5*H*)-phenanthridinone (IIc).

The nitro derivative (IIa) (4.0 g., 0.01 mole), toluene (2 l.), 95% ethanol (1 l.), 85% hydrazine hydrate (10 ml.) and Raney nickel (~100 mg.) were mixed, heated, and boiled with the occasional addition of Raney nickel (in ~100 mg. portions) for 30 minutes. A second portion of 85% hydrazine hydrate (5 ml.) was then added. Boiling was continued for 20 minutes and the reaction mixture was filtered hot. The filtrate was concentrated until crystallization of the amine took place giving 2.3 g. (63%); ir cm^{-1} , ν max (-CONH-) 3150, 1650; (two adjacent hydrogens) 825.

2-Amino-3,8-dichloro-6(5*H*)-phenanthridinone (II d).

Reduction of IIb (3.1 g., 0.01 mole) in the same manner as described in the preceding paragraph gave 2 g. (72%) of the amine; ir cm^{-1} , ν max (-CONH-) 3200, 1650; (two adjacent hydrogens) 825.

3-Amino-8-chloro-2-nitro-6(5*H*)-phenanthridinone (IIe).

2-Amino-7-chloro-3-nitro-9-oxofluorene.

N-(7-Chloro-3-nitro-9-oxo-2-fluorenyl)acetamide (12) (3.8 g., 0.012 mole), absolute ethanol (500 ml.) and concentrated hydrochloric acid (200 ml.) were mixed, vigorously refluxed with stirring for 2 hours, and then most of the solvent was distilled off leaving a pasty purple residue which was diluted with water and basified with concentrated ammonium hydroxide. After filtration and drying, the amine, 3.3 g. (100%), was recrystallized from toluene giving thin purple needles, m.p., 309-310°; ir cm^{-1} , ν max (C=O) 1710; (NO_2) 1325; (two adjacent hydrogens) 828.

Anal. Calcd. for $\text{C}_{13}\text{H}_7\text{ClN}_2\text{O}_3$: C, 56.85; H, 2.57; N, 10.20. Found: C, 56.72; H, 2.57; N, 10.07.

The above amine (1.4 g., 5 mmoles) was stirred in concentrated sulfuric acid (60 ml.) until dissolution occurred. It was then

chilled in an ice bath and, with constant stirring, a saturated aqueous solution of sodium azide (1.0 g., 15 mmoles) was introduced in small drops over a half-hour period. After further stirring in the cooling bath for 2 hours and at ambient temperature for 24 hours the reaction solution was poured over crushed ice. The mixture was carefully neutralized with dilute sodium hydroxide and the flocculent precipitate was collected on a filter. It was washed thoroughly with water, dried (1.45 g., 100%), and recrystallized from acetone-acetic acid giving tiny orange-yellow needles; ir cm^{-1} , ν max (-CONH-) 3300, 1650; (NO_2) 1335; (two adjacent hydrogens) 825.

8-Chloro-2-nitro-6(5H)-phenanthridinone (IIf).

(a) From Nitration of 8-Chloro-6(5H)-phenanthridinone.

8-Chloro-6(5H)-phenanthridinone (If) (1.9 g., 9 mmoles) was added in small portions to a stirred mixture of acetic acid (25 ml.) and 90% nitric acid (25 ml.) at 20-25° over a 10-minute period. After all the chloro derivative had been added the mixture was continuously stirred at the same temperature for another 10 minutes and then set aside with occasional stirring for 30 minutes. The crystalline product was filtered off, washed thoroughly with water and dried giving 1.6 g. (73%). Recrystallization from acetone gave light yellow crystals; ir cm^{-1} , ν max (-CONH-) 3200, 1650; (NO_2) 1335; (two adjacent hydrogens) 833.

(b) From Deamination of IIe.

3-Amino-8-chloro-2-nitro-6(5H)-phenanthridinone (Iie) (0.5 g.) was diazotized in concentrated sulfuric acid (5 ml.) with nitrosyl sulfuric acid, prepared from sodium nitrite (0.2 g.) and sulfuric acid (2 ml.), at 25°. The diazotization mixture was allowed to stand for three hours, with occasional stirring; crushed ice (20 g.) was then added and 95% ethanol (20 ml.), and the mixture was stirred until evolution of gas ceased. The next morning the product was collected on a filter giving 0.4 g., m.p. > 360°. The infrared spectrum of this compound and that of the product obtained in (a) above are identical.

(c) From Rearrangement of 7-Chloro-3-nitro-9-oxofluorene.

7-Chloro-3-nitro-9-oxofluorene.

N-(7-Chloro-3-nitro-9-oxo-2-fluorenyl)acetamide (12) (29.9 g., 0.094 mole) was heated in concentrated sulfuric acid (150 ml.) at 90-95° for 1 hour and cooled to 25°. Nitrosyl sulfuric acid, prepared from sodium nitrite (8.5 g., 0.123 mole) and sulfuric acid (50 ml.), was then added portionwise with stirring during a few minutes. This was set aside with occasional stirring for several hours and crushed ice (500 g.) was added and then 95% ethanol (500 ml.). The mixture was stirred until evolution of gas ceased; it was then allowed to stand at ambient temperature overnight. The product was separated by filtration and recrystallized from toluene-ethanol giving 22.9 g. (94%); ir cm^{-1} , ν max (C=O) 1730; (NO_2) 1350; (two adjacent hydrogens) 835.

Anal. Calcd. for $\text{C}_{13}\text{H}_6\text{ClNO}_3$: C, 60.14; H, 2.33; N, 5.40. Found: C, 60.12; H, 2.30; N, 5.34.

The above 9-oxofluorene (2.6 g., 0.01 mole) was reacted with sodium azide (2.0 g., 0.03 mole) in concentrated sulfuric acid (150 ml.) as described previously and the product was recrystallized from acetic acid giving 2.4 g. (87%), m.p. > 360°. Infrared absorptions of this compound and of the products obtained from (a) and (b) are identical.

2-Amino-8-chloro-6(5H)-phenanthridinone (IIg).

A mixture of 8-chloro-2-nitro-6(5H)-phenanthridinone (IIf) (0.1 g.), toluene (100 ml.), 95% ethanol (100 ml.), and 85%

hydrazine hydrate (2 ml.) was boiled with occasional addition of small amounts of Raney nickel for 30 minutes. A second portion of 85% hydrazine hydrate (1 ml.) was then added. The reaction mixture was boiled further for 10 minutes and filtered hot. The filtrate was concentrated until crystallization of the product took place. This was filtered off and recrystallized from ethanol-water giving lustrous yellowish-white needles; ir cm^{-1} , ν max (-CONH-) 3220, 1660; (two adjacent hydrogens) 825.

3-Chloro-2-nitro-6(5H)-phenanthridinone (IIh).

(a) From Nitration of 3-Chloro-6(5H)-phenanthridinone.

3-Chloro-6(5H)-phenanthridinone (13) (2 g., ~ 9 mmoles) was nitrated at 50-55° (10 minutes) with 90% nitric acid (25 ml.) in acetic acid (25 ml.). The product was recrystallized from acetic acid as thin white needles, 1.7 g. (71%); ir cm^{-1} , ν max (-CONH-) 3220, 1670; (NO_2) 1330; (four adjacent hydrogens) 755.

(b) From Rearrangement of 2-Chloro-3-nitro-9-oxofluorene.

2-Chloro-3-nitro-9-oxofluorene.

2-Amino-3-nitro-9-oxofluorene (14) (4.8 g., 0.02 mole) was diazotized in sulfuric acid (30 ml.) with nitrosyl sulfuric acid, prepared from sodium nitrite (1.7 g.) and sulfuric acid (10 ml.), at ambient temperature. After several hours the diazotization mixture was mixed with crushed ice (100 g.) and added to a solution of freshly prepared cuprous chloride (~ 6 g.) in concentrated hydrochloric acid (15 ml.). The mixture was heated on a steam bath for 30 minutes and diluted with water. The crude product was separated and chromatographed through an alumina column with benzene as eluent giving 4.1 g. (79%), m.p. 229.5-230.5°; ir cm^{-1} , ν max (C=O) 1750; (four adjacent hydrogens) 763.

Anal. Calcd. for $\text{C}_{13}\text{H}_6\text{ClNO}_3$: C, 60.13; H, 2.33; N, 5.39; Cl, 13.66. Found: C, 60.27; H, 2.35; N, 5.21; Cl, 13.53.

The above 9-oxofluorene (0.5 g., 2 mmoles), dissolved in sulfuric acid (25 ml.) was treated with sodium azide (0.3 g., ~ 4 mmoles) and water (1 ml.) over a period of 1.5 hours. The reaction solution was then stirred in an ice bath for 1.5 hours and at ambient temperature for 16 hours and diluted with water. Upon separation and recrystallization from acetic acid there was obtained 0.4 g. (76%) of IIh, identical with the material obtained by method (a) as determined by mixture m.p. and by infrared spectra.

Reduction-Debromination of 3,8-Dibromo-2-nitro-6(5H)-phenanthridinone.

3,8-Dibromo-2-nitro-6(5H)-phenanthridinone (IIa) (4 g., 0.01 mole), 85% hydrazine hydrate (10 ml.), 5% palladium-on-charcoal (0.1 g.), and 95% ethanol (500 ml.) were mixed and refluxed with stirring for 6 hours and filtered hot. The filtrate was evaporated until crystallization of yellowish-white blades took place. It was cooled and the blades were collected on a filter, washed with dilute ethanol and dried giving 1.6 g. (76%). Melting point and mixture melting point with an authentic sample showed that the product was 2-amino-6(5H)-phenanthridinone (15), m.p. 283-284°.

Reduction-Dechlorination of 3-Chloro- and 3,8-Dichloro-2-nitro-6(5H)-phenanthridinone.

The chloro-nitro compound (IIb or IIh) was refluxed in 95% ethanol with 5% palladium-on-charcoal and 85% hydrazine hydrate as described above giving 2-amino-6(5H)-phenanthridinone in 92-95% yields.

1-Amino-6(5H)-phenanthridinone (IIIa) (5).

(a) From 4-Amino-9-oxofluorene.

4-Amino-9-oxofluorene (16) (39.0 g., 0.2 mole) was added in small portions to stirred concentrated sulfuric acid (200 ml.) during 10 minutes. The solution was then stirred in an ice bath and a solution of sodium azide (24 g., 0.37 mole) in water (55 ml.) was added dropwise over a period of 6 hours. After the addition of the azide solution had been completed the reaction mixture was continuously stirred in the ice bath for a few more hours and the cooling bath was removed. Stirring was continued for 48 hours and the mixture was diluted with an equal volume of ice water. The amine sulfate was collected on a filter and treated with warm 5% sodium hydroxide (excess). The product was filtered off, washed thoroughly with water and dried giving 41.5 g. (99%), m.p. 290-292°. One recrystallization from 95% ethanol gave white needles, m.p. 293-294° dec.; ir cm^{-1} , ν max (-CONH-) 3200, 1660; (four adjacent hydrogens) 763.

(b) From Reduction of 1-Nitro-6(5*H*)-phenanthridinone.

The nitro compound (0.24 g., 1 mmole), prepared from 4-nitro-9-oxofluorene as described below, was refluxed for 3 hours in 95% ethanol (50 ml.) with 85% hydrazine hydrate (1.5 ml.) and 5% palladium-on-charcoal (50 mg.). The mixture was filtered and evaporation of the filtrate gave the product. Melting point and mixture melting point with the compound obtained in (a), 293-294° dec.

1-Nitro-6(5*H*)-phenanthridinone (IIIb) (5).

4-Nitro-9-oxofluorene (9) (2.3 g., 0.01 mole) in concentrated sulfuric acid (40 ml.) was treated with sodium azide (1.2 g., 0.018 mole) (40 hours) as described in previous experiments giving 2.3 g. (96%) of the product which was recrystallized from acetic acid; ir cm^{-1} , ν max (-CONH-) 3200, 1660; (NO_2) 1365; (four adjacent hydrogens) 752.

1-Chloro-3-nitro-6(5*H*)-phenanthridinone (IIIc).

A solution of 4-chloro-2-nitro-9-oxofluorene (17) (10 g., 0.038 mole) in concentrated sulfuric acid (150 ml.) was reacted with sodium azide (4.6 g., 0.07 mole) (26 hours) in the usual manner giving 10.4 g. of a yellowish solid which was recrystallized once from acetone and twice from acetic acid giving thin needles, 7.4 g. (71%); ir cm^{-1} , ν max (-CONH-) 3220, 1670; (NO_2) 1350; (four adjacent hydrogens) 746.

10-Chloro-8-nitro-6(5*H*)-phenanthridinone (IV).

2-(2'-Chloro-4'-nitrophenyl)benzoic acid.

Copper powder (450 A; Metal Disintegrating Co.) (100 g.) was added in small portions to a rapidly stirred mixture of 3-chloro-4-iodonitrobenzene (18) (113.5 g., 0.4 mole) and methyl 2-bromobenzoate (EK white label) (86 g., 0.4 mole) at 200° over a period of 30 minutes. After all the copper powder had been added the reaction mixture was stirred at 210-215° for 10 minutes and cooled. The contents were extracted with acetone. Evaporation of the acetone gave a black oil which was extracted with boiling ligroin (d. 0.68-0.70). After removal of the solvent the amber residual oil was dissolved in benzene and passed through an alumina column. The fast moving orange band was washed down with the same solvent. Evaporation of the benzene gave 69.7 g. of methyl 2-(2'-chloro-4'-nitrophenyl)benzoate as an amber oil. The methyl ester was mixed with acetic acid (500 ml.), sulfuric acid (250 ml.), and water (125 ml.). The mixture was vigorously refluxed for 28 hours, cooled, and diluted with ice water. The gummy precipitate was separated and water-washed by decantation, boiled for 3 hours in 15% sodium carbonate (1500 ml.) and filtered. The filtrate was shaken with chloroform (200 ml.) and the aqueous layer was separated and acidified with concentrated hydrochloric acid giving

33.7 g. of crude product (30% based on the iodo compound used). Recrystallization from boiling water gave light yellow crystals, m.p. 195-197° dec.; ir cm^{-1} , ν max (COOH) 3080, 1720; (NO_2) 1350; (two adjacent hydrogens) 838; (four adjacent hydrogens) 770.

Anal. Calcd. for $\text{C}_{13}\text{H}_8\text{ClNO}_4$: C, 56.23; H, 2.90; N, 5.05; Cl, 12.77. Found: C, 56.13; H, 2.88; N, 4.92; Cl, 12.78.

2-(2'-Chloro-4'-nitrophenyl)aniline.

The above acid (13.9 g. 0.05 mole) was dissolved in a mixture of concentrated sulfuric acid (80 ml.) and 20% oleum (20 ml.). The mixture was covered with chloroform (200 ml.) and solid sodium azide (4.6 g., 0.07 mole) was added in small amounts, with stirring, at such a rate as to maintain the temperature of the reaction mixture at 40-42° (40 minutes). After all the azide had been added the mixture was continuously stirred at the same temperature for 2 hours and then at room temperature for 16 hours and the acid layer was separated. It was stirred into a mixture of crushed ice and water and basified with concentrated aqueous sodium hydroxide. The amine was filtered off, washed with water and dried giving 11.2 g. (90%), m.p. 110-114°. Recrystallization from ethanol-water gave orange-yellow needles, m.p. 117-118°; ir cm^{-1} , ν max (NO_2) 1350; (two adjacent hydrogens) 833; (four adjacent hydrogens) 768.

Anal. Calcd. for $\text{C}_{12}\text{H}_9\text{ClN}_2\text{O}_2$: C, 57.96; H, 3.65; N, 11.27. Found: C, 58.16; H, 3.65; N, 11.29.

The above amine (2.5 g., 0.01 mole) in toluene (15 ml.) was added portionwise with stirring to a mixture of phosgene (5 g., 0.05 mole) and toluene (15 ml.) (ice bath) over a period of 5 minutes. The mixture was gently refluxed for 3 hours and stripped of the solvent while a stream of phosgene was bubbled through the solution. The residual oil solidified upon drying over phosphorus pentoxide in a vacuum giving the 2-(2'-chloro-4'-nitrophenyl)phenylisocyanate, 2.8 g. (100%), m.p. 84-85°, which was not purified further and was used directly in the next step.

The isocyanate (2.8 g., 0.01 mole) was dissolved in chlorobenzene (10 ml.) and added dropwise (10 minutes) to a stirred mixture of anhydrous aluminum chloride (2 g., 0.015 mole) in chlorobenzene (10 ml.). The mixture was stirred first at 50-60° for 30 minutes and then at 90-95° for 2 hours and cooled. It was diluted with ice water and the chlorobenzene was steam-distilled. The aqueous mixture was cooled in ice. The yellow solid was separated, washed with water, and recrystallized from 95% ethanol with Darco giving yellowish crystals of IV, 0.5 g. (19%); ir cm^{-1} , ν max (-CONH-) 3350, 1700; (NO_2) 1345; (four adjacent hydrogens) 746.

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