

36. *The Synthesis of Indenoquinolines.*

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Application of the Skraup, Döbner-Miller, Döbner cinchoninic acid, or Combes reaction to 2-aminofluorene results in ring-closure at the 3-position yielding indeno(3' : 2'-6 : 7)quinolines. Oxidation of 3-azachrysene gives 3-azachrysene-7 : 8-quinone, which undergoes the benzylic acid rearrangement to give the valuable reference compound 1'-oxoindeno(2' : 3'-5 : 6)-quinoline.

THE products of ring-closure of 2-aminofluorene derivatives have been rigidly orientated in only two cases, cyclisation occurring in the 1-position in one instance and the 3-position in the other.¹ It was therefore desirable to effect other cyclisations and orientate the products.

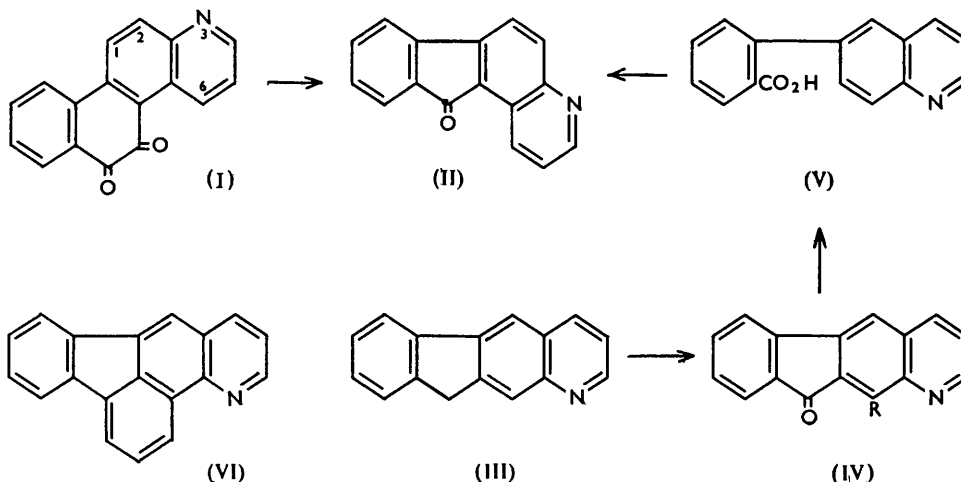
2-Aminofluorene undergoes the Skraup reaction to give an indenoquinoline (III),² which we have orientated in the following manner. 3-Azachrysene was oxidised to the 7 : 8-quinone (I) which with alkali underwent the benzylic acid rearrangement to give a substance which must be 1'-oxoindeno(2' : 3'-5 : 6)quinoline (II) and is different from the ketone (IV; R = H) obtained by oxidation of Diels's indenoquinoline. The Diels compound must therefore be indeno(3' : 2'-6 : 7)quinoline (III). This conclusion is valid, however, only if the structure assigned to the quinone (I) is correct. It is possible that oxidation of 3-azachrysene occurs at C₍₁₎ and C₍₂₎ of the chrysene molecule to give 3-azachrysene-1 : 2-quinone, which would undergo the benzylic acid rearrangement to give not an oxoindenoquinoline but 8-aza-1 : 2-benzofluorenone. Now the Diels indenoquinoline (III) is oxidised to the keto-compound (IV; R = H) which on fission with alkali and subsequent ring-closure yields an oxoindenoquinoline different from the starting ketone but identical with 1'-oxoindeno(2' : 3'-5 : 6)quinoline (II). These observations can be accounted for only by assigning to the azachrysenequinone and the Diels indenoquinoline structures (I) and (III), respectively. The conversion of the Diels indenoquinoline (III) into 1'-oxoindeno(2' : 3'-5 : 6)quinoline (II) must proceed through the acid (V) in which

¹ Bremer and Hamilton, *J. Amer. Chem. Soc.*, (a) 1951, **73**, 1844; (b) Campbell and Stafford, *J.*, 1952, 299.

² Diels and Staehlin, *Ber.*, 1902, **35**, 3275.

the carboxyl group is attached to the benzene and not to the quinoline ring, since otherwise ring-closure would have afforded the original oxoindenoquinoline (IV; R = H).

There can thus be no doubt that the Skraup reaction with 2-aminofluorene involves ring-closure at position 3. This confirms the conclusion reached earlier from spectroscopic evidence,^{1b} and shows that the angular structure tentatively assigned by Clemo and Felton³ is erroneous. Further confirmation is supplied by a comparison of the spectra



of the two oxoindenoquinolines with those of 1 : 2- and 2 : 3-benzofluorenone (Figs. 1 and 2) which show much greater differences than do the corresponding benzofluorenes. It is clear from the absorption curves that the spectrum of 1'-oxoindeno(3' : 2'-6 : 7)quinoline resembles that of 2 : 3-benzofluorenone, whilst the spectra of 1'-oxoindeno(2' : 3'-5 : 6)quinoline and 1 : 2-benzofluorenone are very similar.

The Skraup reaction of 2-amino-3-nitrofluorene gave a very dirty product from which only a very small quantity of 1'-oxoindeno(3' : 2'-6 : 7)quinoline (IV) could be obtained. This displacement of a nitro-group is found in the formation of 5 : 6-benzoquinoline from 1-nitro-2-naphthylamine.⁴

A synthesis of 1'-oxoindeno(3' : 2'-6 : 7)quinoline was attempted by Skraup reaction from 4-aminofluoranthene. However, the product, pyrido(3' : 2'-3 : 4)fluoranthene (VI), was obtained in such poor yield that oxidation to the acid (IV; R = CO₂H) was not tried.

Neish⁵ obtained an indenoquinoline derivative by heating 2-aminofluorene with pyruvic acid, and tentatively suggested that it is an indeno(2' : 3'-5 : 6)quinoline. Decarboxylation of the 4-carboxylic acid yielded 2-methylindeno(3' : 2'-6 : 7)quinoline (VIII), which was oxidised by selenium dioxide to the aldehyde. Oxidation of the aldehyde with hydrogen peroxide afforded the acid, decarboxylation of which gave indeno(3' : 2'-6 : 7)quinoline (III), identical with the compound already orientated. Neish's product is therefore 2-methylindeno(3' : 2'-6 : 7)quinoline-4-carboxylic acid (VII), its formation furnishing another example of 2-aminofluorene's undergoing ring-closure at the 3-position.

2-Aminofluorene-9-ol with pyruvic acid also underwent ring-closure at the 3-position to give 1'-hydroxy-2-methylindeno(3' : 2'-6 : 7)quinoline-4-carboxylic acid, whose structure followed from the conversion of the acid into 2-methylindeno(3' : 2'-6 : 7)quinoline (VIII) by heating it with lime. Curiously enough, decarboxylation in boiling quinoline

³ Clemo and Felton, *J.*, 1952, 1658.

⁴ Lellmann and Schmidt, *Ber.*, 1887, **20**, 3154.

⁵ Neish, *Rec. Trav. chim.*, 1948, **67**, 349.

with copper yielded the oxoindenoquinaldine, which by Wolff–Kishner reduction gave 2-methylindeno(3' : 2'-6 : 7)quinoline (VIII).

Hughes *et al.*⁶ from the Döbner–Miller reaction of 2-aminofluorene isolated a product of indefinite melting point. Repetition of the work gave 2-methylindeno(3' : 2'-6 : 7)quinoline (VIII), identical with a sample prepared as just described. 2-Aminofluorene with pyruvic acid and benzaldehyde gives a product⁶ which in view of our other results

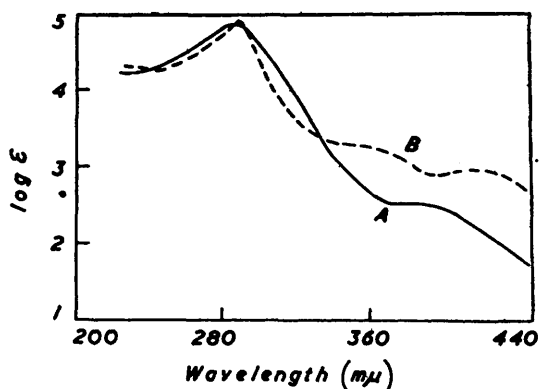
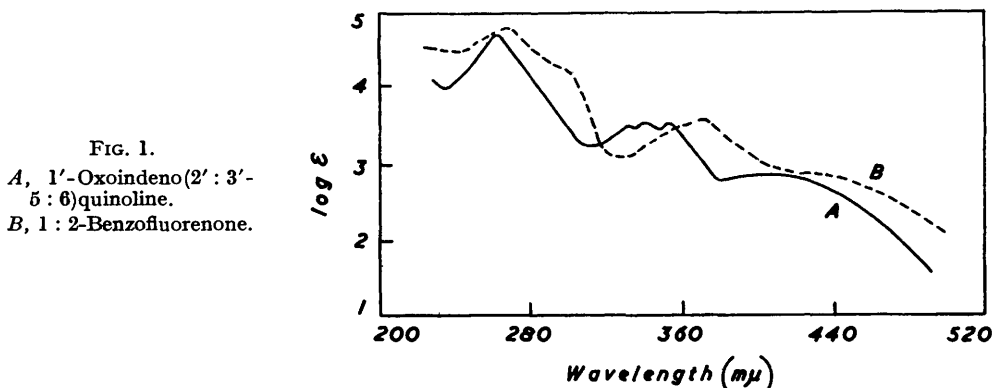
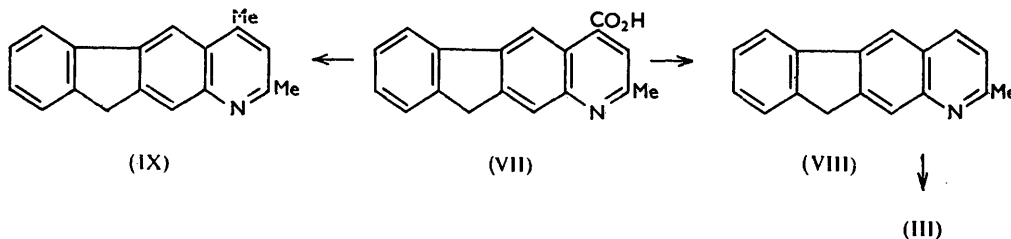


FIG. 2.
A, 1'-Oxoindeno(3' : 2'-6 : 7)quinoline.
B, 2 : 3-Benzofluorenone.

is probably 2-phenylindeno(3' : 2'-6 : 7)quinoline-4-carboxylic acid. Decarboxylation gives the corresponding 2-phenylindenoquinoline whose absorption spectrum above 350 $m\mu$ differs from that of indeno(3' : 2'-6 : 7)quinoline.



2-Aminofluorene and acetylacetone are reported to yield 2 : 4-dimethyl(3' : 2'-6 : 7)quinoline but no structural proof was given.⁷ We have shown that this structure is correct by obtaining it by reducing methyl 2-methylindeno(3' : 2'-6 : 7)quinoline-4-carboxylate (as VII) with lithium aluminium hydride to the 4-hydroxymethyl compound and distilling this with zinc.

⁶ Hughes *et al.*, *J. Proc. Roy. Soc., N.S.W.*, 1938, **71**, 449.

⁷ Buu-Hoi and Royer, *Bull. Soc. chim. France*, 1946, 379.

All the bromine atoms in the bromofluorenes can be removed by cuprous cyanide-pyridine at 280°.⁸ We now find that hydriodic acid removes bromine from the 3- but not the 2-position. 2 : 3 : 7-Tribromofluorene thus yields 2 : 7-dibromofluorene and 2-amino-3 : 7-dibromofluorene gives 2-amino-7-bromofluorene whereas 2-bromo- and 2 : 7-dibromofluorene are unchanged.

Improved methods for the preparation of 2-aminofluorene, 2-amino-7-bromofluorene, and 2-amino-3 : 7-dibromofluorene are described.

EXPERIMENTAL

M. p.s were determined on a Kofler block; chromatographic separations were effected on alumina; fluorescence observations were made under a Hanovia ultraviolet lamp.

2-Aminofluorene.—The following method is more reliable for the preparation of this substance than that described by Kuhn.⁹ Finely divided iron powder (10 g.) was added to a vigorously boiling suspension of 2-nitrofluorene (12.5 g.) in ethanol (180 ml.). Concentrated hydrochloric acid (250 ml.) was added dropwise (1½ hr.) and the solution was boiled (2 hr.). The cooled mixture deposited the amine hydrochloride, which was washed with a little ethanol, and with alkali yielded 2-aminofluorene (89—96%), m. p. 125—126° after crystallisation from ethanol (charcoal). Hydrogenation of 2-nitrofluorene (5 g.) suspended in ethyl acetate (200 ml.) with Raney nickel at room temperature and 60 lb./sq. in. gave 2 : 2'-azoxyfluorene (82%), m. p. 277—279° (lit., 279°).

3-Azachrysen-7 : 8-quinone.—Sodium azide (1.0 g.) was added to 2-acetylphenanthrene (2.2 g.) in trichloroacetic acid (15 g.) and the mixture heated (4 hr.) at 60° (bath temp.). More sodium azide (0.2 g) was added and heating continued (3 hr.); the mixture when poured on ice (50 g.) gave 2-acetamidophenanthrene (72%), needles (from ethanol), m. p. 225—226°. Hydrolysis, by means of methanol (100 ml.) and concentrated hydrochloric acid (15 ml.), and subsequent treatment with alkali gave 2-aminophenanthrene (92%), m. p. 85°. 2-Aminophenanthrene (5.0 g.), glycerol (11 g.), concentrated sulphuric acid (7 ml.), and arsenic pentoxide (9.0 g.) were boiled (4 hr.), poured into water, and the precipitate boiled with hydrochloric acid (charcoal). Treatment with alkali yielded 3-azachrysen (69%), m. p. 129—130°, after crystallisation from toluene. Chromic anhydride ("AnalaR"; 0.1 g.) in water (1 ml.) was added to 3-azachrysen (0.1 g.) in acetic acid (5 ml.) and boiled (2—3 min.). The solvent was removed in a vacuum and the residue extracted with water. The water-insoluble material when sublimed at 190°/0.01 mm. or crystallised from xylene—light petroleum gave slightly impure 3-azachrysen-7 : 8-quinone (10%), crimson needles, m. p. 285—286°.

1'-Oxoindeno(2' : 3'-5 : 6)quinoline.—A suspension of quinone (0.02 g.) in 5% potassium hydroxide (6 ml.) was heated on the water-bath for 36 hr., a stream of air being blown through the mixture. Evaporation in a vacuum to half volume gave 1'-oxoindeno(2' : 3'-5 : 6)quinoline (50%), yellow needles (from ethanol), m. p. 178—179° (Found : C, 83.2; H, 4.1; N, 5.8. C₁₆H₉ON requires C, 83.1; H, 3.9; N, 6.1%). A mixture with the ketone, m. p. 190°, obtained by oxidising the Diels indenoquinoline melted over a range below 170°.

Conversion of 1'-Oxoindeno(3' : 2'-6 : 7)quinoline into 1'-Oxoindeno(2' : 3'-5 : 6)quinoline.—The oxoindenoquinoline (1 g.) was added in small quantities to a stirred mixture of potassium hydroxide (3 g.) and diphenyl ether (30 ml.) at 180° and kept at this temperature for 2 hr. The mixture was poured into benzene, and the precipitated potassium salt was removed. This was added to cold concentrated sulphuric acid (3 ml.) and was then heated to 100° for 1 hr. Pouring the mixture into water and treating with alkali yielded 1'-oxoindeno(2' : 3'-5 : 6)quinoline, m. p. 178—179°, not depressed when mixed with the above oxoindenoquinoline obtained from azachrysenquinone.

Indeno(2' : 3'-5 : 6)quinoline.—The oxoindenoquinoline (0.2 g.) was boiled (2 hr.) in trimethylene glycol (10 ml.) with 90% hydrazine hydrate (0.5 ml.) and sodium hydroxide (0.1 g.). The condenser was removed until the temperature of the mixture reached 205°, the condenser was then replaced and boiling continued for 2 hr. The solution was concentrated in a vacuum, poured into water, and extracted with ether. The dried extract (Na₂SO₄) on evaporation yielded an oil, which was converted into the picrate. The benzene solution obtained by shaking the picrate with benzene and aqueous sodium hydroxide was chromatographed. A white

⁸ Campbell, McKail, and Muir, *Chem. and Ind.*, 1952, 739.

⁹ Kuhn, *Org. Synth.*, 13, 74; cf. Gray, Hartley, and Ibbotson, *J.*, 1955, 2686.

fluorescent band on elution with benzene yielded *indeno*(2' : 3'-5 : 6)*quinoline*, needles, m. p. 150°, from benzene and light petroleum (Found : C, 88.5; H, 5.2; N, 6.0. $C_{16}H_{11}N$ requires C, 88.5; H, 5.1; N, 6.4%).

Skraup Reaction of 2-Amino-3-nitrofluorene.—The fluorene (2.0 g.), glycerol (9.0 g.), arsenic pentoxide (4.6 g.), and concentrated sulphuric acid (2.0 g.) were heated (3 hr.). The mixture was poured into water, and the tarry precipitate dried in a vacuum (P_2O_5). Extraction of this material with benzene for 3 hr. gave a dark solution which was chromatographed. Development with benzene gave a yellow band which on elution yielded 1'-oxoindeno(3' : 2'-6 : 7)*quinoline* (2%), m. p. and mixed m. p. 187—189°.

Pyrido(3' : 2'-3 : 4)*fluoranthene*.—4-Aminofluoranthene (3 g.), glycerol (12.6 g.), concentrated sulphuric acid (4.0 g.), and arsenic oxide (6.4 g.) were heated for 6 hr. and the whole poured into water. Treatment with excess of alkali, extraction with ether (2×100 ml.), and removal of the ether gave a product which was chromatographed in benzene. The eluate yielded *pyrido*(3' : 2'-3 : 4)*fluoranthene* (12%), pale yellow needles (from ethanol), m. p. 169—170° (Found : C, 90.2; H, 4.3; N, 5.8. $C_{19}H_{11}N$ requires C, 90.1; H, 4.4; N, 5.5%).

Constitution of 2-Methylindeno(3' : 2'-6 : 7)*quinoline-4-carboxylic Acid*.—The acid was prepared by Neish's method⁵ and gave a *methyl ester*, needles (from methanol), m. p. 168—170° (Found : C, 78.3; H, 5.3; N, 4.9. $C_{19}H_{15}O_2N$ requires C, 78.9; H, 5.2; N, 4.8%). The acid was decarboxylated by heating it with calcium oxide. A red oil distilled and when chromatographed in benzene solution gave a brilliant white fluorescent zone from which 2-methylindeno(3' : 2'-6 : 7)*quinoline* was separated; this formed needles (from benzene and light petroleum), m. p. 169—170° (lit., 151—152°). The methylindenoquinoline (0.5 g.) was boiled (3 hr.) with freshly prepared selenium dioxide (0.5 g.) in dioxan (70 ml.) and water (5 ml.). Charcoal (0.2 g.) was added and the boiling solution filtered hot. The solution was evaporated to half-bulk and water was added until a permanent precipitate separated. This precipitate was dissolved in boiling ethanol and a small quantity of mercury was added to assist in separating the selenium, and the solution was boiled (1 hr.). Charcoal was added and the boiling solution filtered. Reduction of the volume yielded the *aldehyde* (40%), needles, m. p. 221—222° (Found : C, 83.2; H, 4.6; N, 5.6. $C_{17}H_{11}ON$ requires C, 83.3; H, 4.5; N, 5.7%). The aldehyde (0.3 g.), acetone ("AnalaR"; 200 ml.), and hydrogen peroxide (30%, 2 ml.) were boiled (3 hr.). Removal of the solvent afforded *indeno*(3' : 2'-6 : 7)*quinoline-2-carboxylic acid* (57%), yellow crystals (from acetic acid), m. p. 238—239° (Found : C, 77.7; H, 4.6; N, 5.4. $C_{17}H_{11}O_2N$ requires C, 78.2; H, 4.3; N, 5.4%). Heating the acid (0.1 g.) with calcium oxide (0.6 g.) yielded an oil which was chromatographed in benzene. Development with benzene gave a brilliant white fluorescent zone, which yielded *indeno*(3' : 2'-6 : 7)*quinoline*, m. p. and mixed m. p. 132—133°.

1'-Hydroxy-2-methylindeno(3' : 2'-6 : 7)*quinoline-4-carboxylic Acid*.—2-Aminofluoren-9-ol (3 g.) was boiled (5 hr.) in the minimum volume of ethanol with pyruvic acid (3 ml.). The quinaldinic acid (40%) separated, but was not obtained pure; it had m. p. 300—310° after crystallisation from nitrobenzene. It formed a *methyl ester*, m. p. 227—228° (Found : C, 74.0; H, 5.0; N, 5.1. $C_{19}H_{15}O_3N$ requires C, 74.7; H, 5.0; N, 4.6%). The acid (1 g.) was boiled for 2 hr. in quinoline (10 ml.) with copper (0.01 g.). The quinoline was removed by steam distillation and a benzene solution of the black residue was chromatographed. Development with benzene gave a yellow zone which on elution yielded 2-methyl-1'-oxoindeno(3' : 2'-6 : 7)*quinoline*, yellow needles (0.35 g.) (from benzene-light petroleum), m. p. 203—204° (Found : C, 83.2; H, 4.5; N, 5.6. $C_{17}H_{11}ON$ requires C, 83.3; H, 4.5; N, 5.7%). It formed a crimson, high-melting 2 : 4-*dinitrophenylhydrazone* (Found : N, 16.8. $C_{23}H_{15}O_4N_5$ requires N, 16.5%). Decarboxylation of the acid by heating it with calcium oxide yielded *indeno*(3' : 2'-6 : 7)*quinoline*, m. p. and mixed m. p. 168—169°, which was also obtained by boiling the oxoindenoquinoline with hydrazine hydrate in trimethylene glycol.

Döbner-Miller Reaction of 2-Aminofluorene.—2-Aminofluorene (2.1 g.), concentrated hydrochloric acid (4 ml.), paraldehyde (3 g.), and zinc chloride (1.5 g.) were warmed on the water-bath for 90 min. The dark red oil was poured into water (20 ml.) containing sodium hydroxide (5 g.). The dark material was washed with water and extracted with benzene. The washed benzene solution was reduced to small bulk and chromatographed. Development with benzene gave a zone with a brilliant white fluorescence, which on elution yielded 2-methylindeno(3' : 2'-6 : 7)*quinoline* (10%), needles (from benzene-light petroleum), m. p. and mixed m. p. 168°

2 : 4-Dimethylindeno(3' : 2'-6 : 7)quinoline.—We were unable to prepare this compound by Buu-Hoï and Royer's method⁷ since sulphonation occurred. The following method is advantageous on the small scale. The anil (1 g.) obtained from 2-aminofluorene and acetyl-acetone was added to polyphosphoric acid made by dissolving phosphorus pentoxide (10 g.) in glacial phosphoric acid (10 ml.), and the whole heated on a boiling-water bath until it became a deep yellow. Pouring the solution into water and adding excess of alkali gave a product which was extracted with ether (2 × 100 ml.). Evaporation of the ether yielded 2 : 4-dimethyl-(3' : 2'-6 : 7)quinoline (79%), prisms (from benzene-light petroleum), m. p. 158°.

Methyl 2-methylindeno(3' : 2'-6 : 7)quinoline-4-carboxylate (0.5 g.) in dry benzene ("AnalaR"; 100 ml.) was added to lithium aluminium hydride (0.5 g.) in dry ether (200 ml.), and the whole boiled for 2 hr. after which solvent (200 ml.) was removed. Water (100 ml.) containing sodium hydroxide (1 g.) was cautiously added and the remaining organic solvent was distilled off. Impure 4-hydroxymethyl-2-methylindeno(3' : 2'-6 : 7)quinoline (71%), m. p. 225—227°, separated, and the dried compound (1 g.) was heated with zinc dust (6 g.). The red distillate was dissolved in benzene and chromatographed. Development with benzene gave a solution which on evaporation yielded 2 : 4-dimethylindeno(3' : 2'-6 : 7)quinoline (20%), prisms (from benzene-light petroleum), m. p. and mixed m. p. 158°.

2-Phenylindenoquinoline.—A boiling solution of 2-aminofluorene (3.0 g.) in ethanol (10 ml.) was gradually added to a boiling solution of pyruvic acid (1.1 g.) and benzaldehyde (2.0 g.) in ethanol (25 ml.). After 1 hr. 2-phenylindenoquinoline (65%), m. p. 265—270°, was obtained and when decarboxylated by heating in quinoline with copper or preferably by distillation from lime yielded 2-phenylindenoquinoline (40%), m. p. 222—223° (Found: C, 89.6; H, 5.0; N, 5.4. $C_{22}H_{15}N$ requires C, 90.0; H, 5.2; N, 4.8%).

Debromination Experiments.—The bromo-compound (1 g.) was boiled for 4 hr. with hydriodic acid (7 ml.; d 1.94) and red phosphorus (0.2 g.), and the whole poured into 2% potassium iodide solution (100 ml.). The product was purified by crystallisation from ethanol. 2-Bromo- and 2 : 7-dibromo-fluorene thus treated were unchanged; but 2 : 3 : 7-tribromofluorene gave 2 : 7-dibromofluorene (85%), m. p. and mixed m. p. 162°, and 2-amino-3 : 7-dibromofluorene gave 2-amino-7-bromofluorene, isolated as the acetyl derivative (85%), m. p. and mixed m. p. 231°.

2-Amino-3 : 7-dibromofluorene.—Fluorene was brominated in chloroform at 0° giving 2-bromofluorene contaminated with 2 : 7-dibromofluorene. The crude 2-bromofluorene (60 g.) in acetic acid (500 c.c.) was treated at 50° with concentrated nitric acid (500 c.c.) and the temperature gradually raised to 80° and kept at this temperature for 5 min. The mixture was cooled to room temperature, and the precipitate was separated, and washed with a little acetic acid and then a large volume of water. Crystallisation from acetic acid gave 2-bromo-7-nitrofluorene (67% yield), m. p. 236° (lit., 236°). Reduction with reduced iron and hydrochloric acid (see preparation of 2-aminofluorene) yielded 2-amino-7-bromofluorene (90%), m. p. 140—141° after crystallisation from aqueous ethanol. The acetyl derivative (10 g.) in nitrobenzene (45 c.c.) and bromine (7 g.) were kept at room temperature (3 hr.). The nitrobenzene was removed by steam-distillation and left 2-acetamido-3 : 7-dibromofluorene (80%), m. p. 272° after crystallisation from acetic acid. The acetamido-compound (10 g.) was boiled (1½ hr.) with 70% sulphuric acid (100 c.c.) and acetic acid (50 c.c.), and then poured on crushed ice. Addition of ammonia gave 2-amino-3 : 7-dibromofluorene (80%), microcrystals, m. p. 133—134° after crystallisation from acetic acid.

Spectroscopic Measurements.—Ultraviolet spectra were measured with a Unicam SP.500 quartz spectrophotometer. The solvent was 95% ethanol. $\log \epsilon$ is given in parentheses. 1'-Oxoindeno(3' : 2'-6 : 7)quinoline: λ_{\max} . 281, 378 $m\mu$ (4.81, 2.49); λ_{\min} . 228, 368 $m\mu$ (4.18, 2.48). 1'-Oxoindeno(2' : 3'-5 : 6)quinoline: λ_{\max} . 266, 325, 340, 355, and 425 $m\mu$ (4.72, 3.31, 3.51, 3.56, 2.84); λ_{\min} . 237, 314, 327, 350, and 380 $m\mu$ (3.97, 3.17, 3.30, 3.42, and 2.77). 2-Phenylindenoquinoline: λ_{\max} . 228, 242, 248, 254, 272, 316, 324, 339, 358, and 370 $m\mu$ (4.02, 3.74, 3.79, 3.89, 4.10, 3.53, 3.59, 3.63, 3.74, and 3.83); λ_{\min} . 227, 240, 245, 250, 256, 301, 318, 331, 348, and 362 $m\mu$ (3.84, 3.69, 3.69, 3.73, 3.86, 3.44, 3.52, 3.56, 3.63, and 3.65).

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