

745. Carcinogenic Nitrogen Compounds. Part XL.¹ Condensed Heterocyclic Derivatives of Fluoranthene.

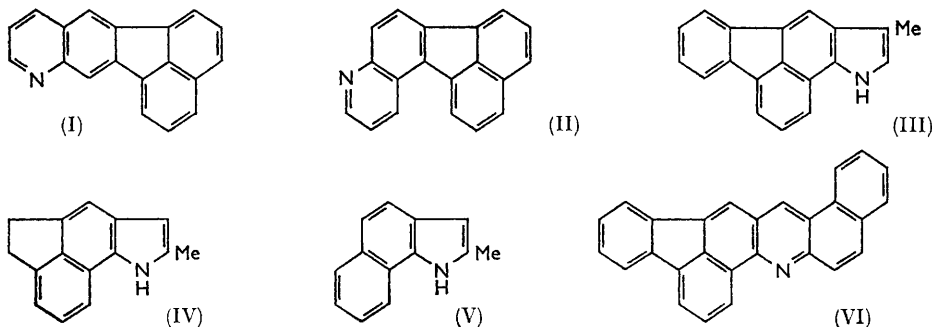
By N. P. BUU-HOÏ, PHILIPPE MABILLE, and JAY BRASCH.

From 3- and 8-aminofluoranthene, a number of condensed heterocycles including pyrrole, indole, quinoline, acridine, phenothiazine, and phenarsazine derivatives bearing the fluoranthene nucleus have been prepared as potential carcinogens; the Skraup reaction with 8-aminofluoranthene gave a linear quinoline rather than the angular one.

ALTHOUGH fluoranthene itself is not carcinogenic, several of its benzo-derivatives are fairly active when painted on the skin or injected,² and 3-acetamidofluoranthene also produces tumours on ingestion.³ On the other hand, the annellation of nitrogenous heterocycles to biologically inactive polycyclic aromatic hydrocarbons often results in carcinogenic compounds.⁴ Hence, it was of interest to prepare, for biological testing, derivatives of fluoranthene bearing various types of five- and six-membered nitrogen-containing rings.

Of the two aminofluoranthenes used as intermediates, the 3-isomer was obtained by reduction (with hydrazine hydrate and Raney nickel) of 3-nitrofluoranthene, the main product in the nitration of the hydrocarbon;⁵ 8-nitrofluoranthene, however, is only a minor product in this last reaction,⁶ and its separation proved impracticable, but the corresponding amine was readily prepared by reduction of the mixtures of 3- and 8-nitrofluoranthene obtained as by-products in the preparation of the 3-isomer, resolution being achieved by crystallisation in ethanol, in which 8-aminofluoranthene is the less soluble isomer.

The Skraup reaction with 8-aminofluoranthene gave a single product which was considered as pyrido(2',3':8,9)fluoranthene (I) rather than the angular isomer (II) on the basis of nuclear magnetic resonance studies. Wolff-Reissert condensation⁷ of 3-aminofluoranthene with chloroacetone gave a poor yield of 5'-methylpyrrolo(3',2':2,3)fluoranthene



(III), most of the amine being converted into a compound whose analyses were consistent with its being an *NN*-difluoranthenylamine, but which did not give, with arsenic trichloride, the phenarsazine cyclisation characteristic of a secondary diarylamine; poor yields were also obtained in the preparation of 5'-methylpyrrolo(3',2':4,5)acenaphthene (IV), from

¹ Part XXXIX, Buu-Hoï, Roussel, and Jacquignon, *J.*, 1964, 708.

² Lacassagne, Buu-Hoï, Zajdela, and Chalvet, Communication to the VIIIth Internat. Cancer Congress, Moscow, 1962; Wynder, *et al.*, cited by Lyons, *Brit. J. Cancer*, 1959, **13**, 126.

³ Schinz, Fritz-Niggli, Campbell, and Schmid, *Oncologia*, 1955, **8**, 233.

⁴ See Buu-Hoï, *Kanzerogenestoffe*, in "Medizinische Grundlagenforsch.," Vol. 2, Georg Thieme Verlag, Stuttgart, 1959, p. 465.

⁵ Kloetzel, King, and Menkes, *J. Amer. Chem. Soc.*, 1956, **78**, 1165.

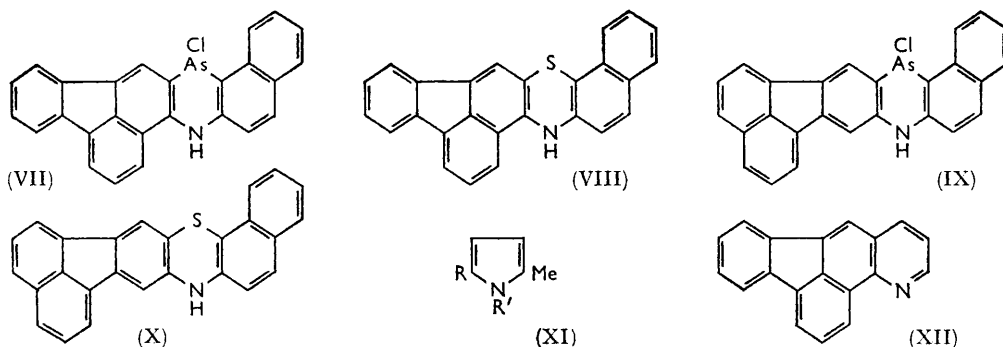
⁶ von Braun and Manz, *Annalen*, 1932, **496**, 170; Garascia, Fries, and Ching, *J. Org. Chem.*, 1952, **17**, 226; Barrett and Buu-Hoï, *J.*, 1958, 4308.

⁷ Wolff, *Ber.*, 1888, **21**, 123, 3360; Reissert and Junghahn, *ibid.*, 1892, **25**, 2699; Verkade and Janetzky, *Rec. trav. chim.*, 1943, **62**, 763.

chloroacetone and 5-aminoacenaphthene. Various changes in the experimental conditions (solvent, temperature, catalyst) failed to improve the yields in this type of reaction, as shown by the data recorded for the condensation of 1-naphthylamine with chloroacetone to give 2-methyl-6,7-benzindole (V).

The iodine-catalysed Knoevenagel condensation⁸ of 3-aminofluoranthene with 2-naphthol readily gave 3-(2-naphthylamino)fluoranthene, but no reaction-product was obtained with 1-naphthol, probably because of steric hindrance. Apparently for the same reason, whereas 3-aminofluoranthene condensed with 2-naphthol and paraformaldehyde⁹ to give the heptacyclic acridine (VI), this synthesis failed with 1-naphthol. Condensation of 3-(2-naphthylamino)fluoranthene with arsenic trichloride and with sulphur afforded the heptacyclic phenarsazine (VII) and the phenothiazine (VIII), respectively. Isomers (IX) and (X) of these last nitrogenous heterocycles were similarly prepared from 8-(2-naphthylamino)fluoranthene.

Both 3- and 8-aminofluoranthene underwent Knorr-Paal reactions¹⁰ with γ -diketones to give the corresponding 1,2,5-trisubstituted pyrroles (XI).



Biological tests showed compound (I) to be sarcomogenic on subcutaneous injection in mice, whereas its isomer (XII) was inactive.

EXPERIMENTAL

Melting points were determined on a Maquenne block.

3- and 8-Aminofluoranthene.—Pure fluoranthene (202.2 g.) was nitrated according to the procedure of Kloetzel *et al.*;⁵ the precipitate obtained at 65° consisted of practically pure 3-nitrofluoranthene (101 g.), m. p. 159—160°. The filtrate deposited, on cooling at 40°, a brown resinous fraction (15 g.) which was discarded, and the liquid was kept overnight at room temperature, giving a precipitate (53 g.), m. p. 100—105°, which was partially purified by one crystallisation from acetone-ethanol (1 : 5). The resulting yellow microcrystalline substance, m. p. 118—123°, was a mixture enriched in 8-nitrofluoranthene, but still containing mostly the 3-isomer. A solution of this mixture (23 g.) and 98% hydrazine hydrate (50 c.c.) in ethanol (1500 c.c.) was refluxed for 2 hr. with Raney nickel (6 g.), the solution concentrated (to 130 c.c.), the nickel filtered off, and the filtrate kept overnight at 0°. The precipitate formed gave 8-aminofluoranthene as greenish-yellow needles (8.5 g.), m. p. 171° (from benzene); 8-acetamidofluoranthene formed golden-yellow prisms, m. p. 206—207° (from benzene) (lit.,⁶ 192.5—193°) (Found: C, 83.2; H, 5.1; N, 5.6. Calc. for C₁₅H₁₃NO: C, 83.4; H, 5.1; N, 5.4%), giving on nitration 3-acetamido-2-nitrofluoranthene, m. p. 293° (from acetic acid) (lit.,⁵ 282—283°). Concentration of the mother-liquors yielded slightly impure 3-aminofluoranthene (10 g.), m. p. 112—115°; the pure compound, prepared in over 90% yield by a similar reduction of 3-nitrofluoranthene, had m. p. 116°.

⁸ Knoevenagel, *J. prakt. Chem.*, 1913, **89**, 30.

⁹ Cf. Ullmann and Fetvadjian, *Ber.*, 1903, **36**, 1029; Buu-Hoï, *J.*, 1946, 792; 1949, 670; 1950, 1146; 1951, 2871.

¹⁰ Knorr, *Annalen*, 1886, **236**, 313; Paal, *Ber.*, 1885, **18**, 2254.

The n.m.r. spectrum of 8-aminofluoranthene, taken in CDCl_3 with an A-60 Varian apparatus, (tetramethylsilane being used as reference) showed the following signals: (a) at *ca.* 3.75 p.p.m., a broad peak corresponding to the protons of the amino-group; (b) at 6.64 p.p.m. (quadruplet, $J = 8.2$ and 2 c./sec.), corresponding to proton 9; at 7.18 p.p.m. (doublet, $J \sim 2$ c./sec.) corresponding to proton 7; (c) between 7.30 and 7.90 p.p.m., corresponding to the seven remaining, unidentified protons. The position of the signal for proton 9 corresponds to the *ortho*-protons in the molecule of aniline, and the mutual coupling ($J \sim 2$ c./sec.) of protons 7 and 9 indicates they are in position *meta* to each other; the shift of the signal of proton 7 (0.54 p.p.m.) towards lower fields as compared with proton 9 could be ascribed to the neighbourhood of aromatic cycle B.

Derivatives of 3-Aminofluoranthene.—3-Benzylideneaminofluoranthene, obtained by refluxing for 30 min. a benzene solution of the amine (4.5 g.) and benzaldehyde (2.2 g.), using a water-trap, formed yellow needles (5.5 g.), m. p. 105° (from ethanol) (Found: C, 90.5; H, 5.1; N, 4.8. $\text{C}_{23}\text{H}_{15}\text{N}$ requires C, 90.5; H, 5.0; N, 4.6%); 3-fluoranthenyliisovaleramide, prepared from the amine (2 g.) and isovaleroyl chloride (1 g.), formed almost colourless prisms (2.5 g.), m. p. 225° (Found: C, 83.7; H, 6.2; N, 4.6. $\text{C}_{21}\text{H}_{19}\text{NO}$ requires C, 83.7; H, 6.4; N, 4.6%); 1-(3-fluoranthenyl)-2-methyl-5-phenylpyrrole, prepared by heating for 30 min. at 180–200° a mixture of the amine (1.1 g.) and phenacylacetone (1.3 g.), formed shiny, pale yellow needles (1.2 g.), m. p. 201° (from ethanol) (Found: C, 90.5; H, 5.6; N, 4.2. $\text{C}_{27}\text{H}_{19}\text{N}$ requires C, 90.7; H, 5.4; N, 3.9%).

Pyrido(2',3':8,9)fluoranthene (I).—A mixture of 8-aminofluoranthene (2.2 g.), glycerol (5 c.c.), arsenic anhydride (2 g.), and sulphuric acid (2 c.c.) was stirred at 165° for 10 min., then maintained at 130–140° for 45 min.; after cooling, the product was extracted thrice with boiling water (750 c.c.), and the aqueous layer filtered, and basified with ammonia. The brown oily precipitate was extracted with hot acetone-ethanol in the presence of charcoal, the organic solution filtered, and the filtrate diluted with water. Recrystallisation of the solid precipitate from heptane afforded orange-yellow needles (0.7 g.), m. p. 168–169°, giving a yellow colour in sulphuric acid (Found: C, 89.9; H, 4.4; N, 5.6. $\text{C}_{19}\text{H}_{11}\text{N}$ requires C, 90.1; H, 4.4; N, 5.5%); the *picrate* formed yellow prisms, m. p. 285–286° (slow decomp. > 220°) (from nitrobenzene) (Found: C, 62.5; H, 3.1; N, 11.7. $\text{C}_{25}\text{H}_{14}\text{N}_4\text{O}_7$ requires C, 62.2; H, 2.9; N, 11.6%). The infrared absorption spectrum showed four strong bands, two between 800 and 900, and two between 1400 and 1500 cm^{-1} . The n.m.r. spectrum provided identification for the following protons: proton 5', at 7.22 p.p.m. (quadruplet, $J = 8.5 \pm 0.2$ and 4.4 ± 0.2 c./sec.); proton 6', at 8.82 p.p.m. (quadruplet, $J = 4.4 \pm 0.2$ and 1.9 ± 0.2 c./sec.); proton 7 or 10, at 8.37 p.p.m. (singlet); signals between 7.42 and 8.08 p.p.m. for the remaining eight protons. The position and coupling constants for protons 5' and 6' are close to those for protons 3 and 2 in the molecule of pyridine (respectively at 7.0 and 8.6 p.p.m., with $J = 7.5$ and 5.5 c./sec.); the presence of a singlet representing one single proton (7 or 10) is in favour of structure (I), as protons 7 and 10 must differ widely from each other in view of the unsymmetrical influence of the nitrogen atom. A Skraup reaction, performed with 3-aminofluoranthene, following the same technique, afforded a 50% yield of pyrido(3',2':3,4)fluoranthene, as pale yellow needles, m. p. 169–170° (lit.¹¹ 169–170°, 12% yield).

5'-Methylpyrrolo(3',2':2,3)fluoranthene (III).—A mixture of 3-aminofluoranthene (3.2 g.), 3-aminofluoranthene hydrochloride (3.5 g.), and chloroacetone (1.5 c.c.) was refluxed for 2.5 hr., the temperature being eventually raised to over 300°; after cooling, the reaction mixture was extracted with hot benzene, and the residue from evaporation of benzene was extracted with heptane. This left a solid, which was recrystallised from benzene, giving golden-yellow leaflets (1.1 g.), m. p. 240° (Found: C, 92.2; H, 4.7; N, 3.4. $\text{C}_{32}\text{H}_{19}\text{N}$ requires C, 92.1; H, 4.6; N, 3.4%); although its composition agreed with that of *NN*-di-(3-fluoranthenyl)amine, this product did not react with arsenic trichloride in boiling *o*-dichlorobenzene, and the initial substance was recovered unchanged. The compound gave a brown *picrate*, m. p. 212°, and a purple-red addition-complex, m. p. 216°, with tetrachlorophthalic anhydride. Concentration of the mother-liquors from crystallisation of the substance, m. p. 240°, yielded the *indole* (III), which formed brownish-yellow prisms (0.4 g.), m. p. 248° (Found: C, 89.9; H, 4.6; N, 5.1. $\text{C}_{19}\text{H}_{13}\text{N}$ requires C, 89.4; H, 5.1; N, 5.5%).

5'-Methylpyrrolo(3',2':4,5)acenaphthene (IV).—A mixture of 5-aminoacenaphthene (2 g.), its hydrochloride (2.4 g.), and chloroacetone (2 c.c.) was refluxed for 1 hr. at 150°, then for 15 min. at 200°; after cooling, the brown solid was extracted with hot benzene, the benzene solution

¹¹ Campbell and Temple, *J.*, 1957, 207.

concentrated, and the precipitate obtained on addition of heptane recrystallised from cyclohexane, giving yellowish *prisms*, m. p. 159° (Found: C, 86.7; H, 6.3. C₁₅H₁₃N requires C, 86.9; H, 6.3%).

Wolff-Reissert Reaction with 1-Naphthylamine.—This was investigated under diverse experimental conditions in order to ascertain which gave the best yields of 2-methyl-6,7-benzindole (V). Results are summarised in the Table.

Ratio amine : chloroacetone	Solvent	Catalyst	Temp.	Time	% Yield
1	Ethanol	None	80°	15 min.	0
1	Ethanol	Pyridine	80	15 min.	0
1	Ethanol	Pyridine	80	30 min.	3.3
2	Acetic acid	ZnCl ₂	118	30 min.	4
1	Ethanol	NaHCO ₃	80	1 hr.	5
2	None	None	100	4 hr.	8
2	None	None	100	36 hr.	11
1	None	Amine-HCl	200	30 min.	17

3-(2-Naphthylamino)fluoranthene.—A mixture of 3-aminofluoranthene (4.4 g.), 2-naphthol (10 g.), and iodine (0.1 g.) was heated for 9 hr. at 200–220°, and the solid obtained on cooling was ground with 10% aqueous sodium hydroxide; the insoluble part was again extracted several times with aqueous sodium hydroxide and finally washed with water. Two crystallisations of the residue from benzene (charcoal) gave pale yellow *leaflets* (3 g.), melting first at 170–171°, and then at 181–182° after resolidification; the benzene solutions showed a strong greenish-yellow fluorescence (Found: C, 90.6; H, 5.1; N, 4.2. C₂₆H₁₇N requires C, 90.9; H, 5.0; N, 4.1%). No condensation product was obtained in an attempt to use 1-naphthol in place of the 2-isomer.

8-(2-Naphthylamino)fluoranthene.—Similarly prepared from 8-aminofluoranthene, this *amine* (4 g.) formed greenish-yellow *prisms*, m. p. 178–179° (from benzene); the benzene solutions likewise showed strong greenish-yellow fluorescence (Found: C, 90.6; H, 5.2%).

16-Chloro-7,16-dihydrobenzo[a]fluoreno[8,9-hi]phenarsazine (VII).—A solution of 3-(2-naphthylamino)fluoranthene (1 g.) and arsenic trichloride (0.5 g.) in *o*-dichlorobenzene (10 c.c.) was refluxed for 30 min.; the precipitate obtained on cooling crystallised from nitrobenzene as greenish-yellow *needles* (0.5 g.), m. p. 320° (decomp.), whose solutions in sulphuric acid were dark violet (Found: C, 69.1; H, 3.3; N, 3.4. C₂₆H₁₅AsClN requires C, 69.1; H, 3.4; N, 3.1%).

Benzo[h]fluoreno[8,9-ab]phenothiazine (VIII).—A mixture of 3-(2-naphthylamino)fluoranthene (1.2 g.) and sulphur (0.2 g.) was heated for 10 min. at 170° with a crystal of iodine; the solid obtained on cooling was extracted with boiling toluene (150 c.c.), which left an undissolved black substance (A). The toluene solution gave, on concentration, a precipitate which was treated with hot acetone (20 c.c.); a small residue of substance (A) was filtered off, and the solid obtained on dilution with water was recrystallised from toluene, giving the *phenothiazine* as golden-yellow *leaflets* (0.3 g.), m. p. 266° (decomp. >200°), whose solutions in sulphuric acid were deep blue (Found: C, 83.5; H, 3.9; N, 4.0. C₂₆H₁₅NS requires C, 83.6; H, 4.1; N, 3.8%). Recrystallisation of substance (A) from toluene gave shiny, blackish violet *needles* (0.2 g.), m. p. 282° (decomp. >250°) (Found: C, 83.1; H, 3.7; N, 3.4; S, 7.9%); this substance contained oxygen, and probably resulted from the phenothiazine by partial oxidation.

Benzo[a]fluoreno[8,9-hi]acridine (VI).—To a boiling mixture of 2-naphthol (6 g.) and 3-aminofluoranthene (6.5 g.), paraformaldehyde (3 g.) was cautiously added in small portions; after the violent reaction had subsided, the resin obtained was distilled *in vacuo*, and the portion boiling at 350–370°/15 mm. was collected, and crystallised first from nitrobenzene, then from toluene, giving shiny, orange-yellow *needles* (2 g.), m. p. 282°, whose solutions in sulphuric acid were yellow (Found: C, 91.6; H, 4.4; N, 4.1. C₂₇H₁₅N requires C, 91.8; H, 4.3; N, 4.0%); the *picrate* formed yellow *prisms*, m. p. 327–328° (decomp. >250°) (from nitrobenzene) (Found: C, 68.2; H, 3.2; N, 9.8. C₃₃H₁₈N₄O₇ requires C, 68.0; H, 3.1; N, 9.6%). No acridine was obtained when 1-naphthol was used in place of 2-naphthol in this reaction.

16-Chloro-7,16-dihydrobenz[a]acenaphthylene[1,2-i]phenarsazine (IX).—Prepared from 8-(2-naphthylamino)fluoranthene as for the isomer (VII), this *phenarsazine* formed shiny, orange-yellow *needles* (0.5 g.), m. p. 365° (decomp. >350°) (from nitrobenzene) (Found: C, 69.0; H, 3.5%); the halochromy in H₂SO₄ was deep violet.

Benzo[h]acenaphthylene[1,2-b]phenothiazine (X).—This *phenothiazine*, prepared as for the

isomer (VIII), formed cream-coloured needles (0.5 g.), m. p. 308° (decomp. > 250°), giving a deep blue colour in sulphuric acid (Found: C, 83.3; H, 4.2%).

1-(8-Fluoranthenyl)-2,5-dimethylpyrrole.—Prepared by refluxing for 20 min. a mixture of hexane-2,5-dione (0.5 g.) and 8-aminofluoranthene (0.4 g.), this *pyrrole* formed shiny yellow leaflets (0.5 g.), m. p. 156° (from acetone-methanol) (Found: C, 89.3; H, 5.9; N, 5.0. $C_{22}H_{17}N$ requires C, 89.5; H, 5.8; N, 4.8%). 1-(8-Fluoranthenyl)-2-methyl-5-phenylpyrrole formed pale yellow leaflets, m. p. 204–205° (from ethanol) (Found: C, 91.0; H, 5.3; N, 4.1%).

This work was supported in part by a research grant from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service, and in part by the Institut National d'Hygiène (Professor L. Bugnard, Paris); we thank the authorities concerned. One of us (J. B.) is indebted to the U.S. Public Health Service for a Research Fellowship.

INSTITUT DE CHIMIE DES SUBSTANCES NATURELLES DU C.N.R.S.,
GIF-SUR-YVETTE (S.-et-O.), FRANCE.

[Received, December 11th, 1963.]
