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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.

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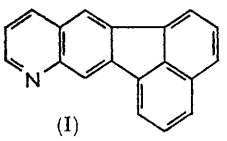
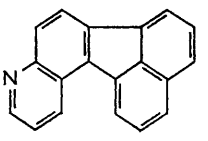
Although fluoranthene itself is not carcinogenic, several of its benzo-derivatives are fairly active when painted on the skin or injected,[2] and 3-acetamidofluoranthene also produces tumours on ingestion.[3] On the other hand, the annellation of nitrogenous heterocycles to biologically inactive polycyclic 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 condensation[7] of 3-aminofluoranthene with chloroacetone gave a poor yield of 5′-methylpyrrolo(3′,2′:2,3)fluoranthene



(I)



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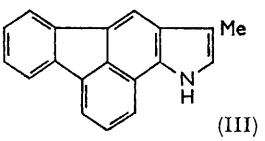

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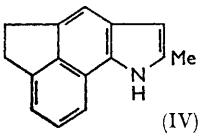

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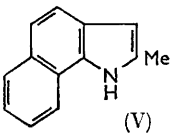

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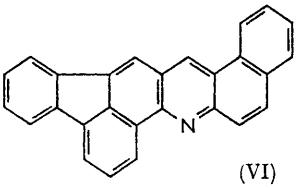

(VI)

(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 Herlag, 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.

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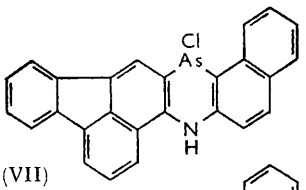
chloroacetone and 5-aminoacenaphthene. Various changes in the experimental conditions (solvent, temperature, catalyst) failed to improve the yields in this type of reaction, as shown by the data recorded for the condensation of 1-naphthylamine with chloroacetone to give 2-methyl-6,7-benzindole (V).

The iodine-catalysed Knoevenagel condensation [8] 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 paraformaldehyde [9] 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 reactions [10] with γ-diketones to give the corresponding 1,2,5-trisubstituted pyrroles (XI).



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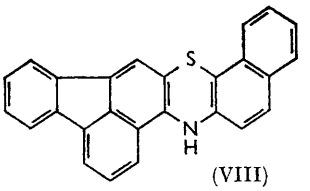

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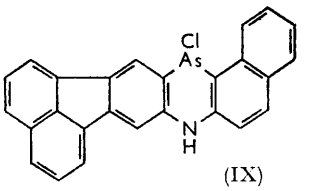

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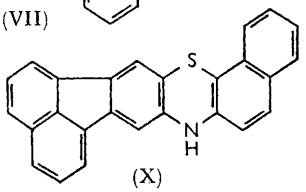

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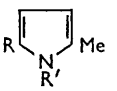
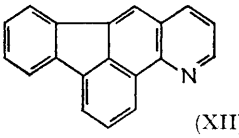


(XI)



(XII)

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 deposed, 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 $C_{18}H_{13}NO$: 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.

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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. $C_{23}H_{15}N$ requires C, 90·5; H, 5·0; N, 4·6%); *3-fluoranthenylisovaleramide*, 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. $C_{21}H_{19}NO$ 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. $C_{27}H_{19}N$ 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. $C_{19}H_{11}N$ 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. $C_{25}H_{14}N_4O_7$ 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 ± 0·2 and 4·4 ± 0·2 c./sec.); proton 6′, at 8·82 p.p.m. (quadruplet, J = 4·4 ± 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. $C_{32}H_{19}N$ 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. $C_{19}H_{13}N$ requires C, 89·4; H, 5·1; N, 5·5%).

5′-Methylσyrrole(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.

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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. $C_{15}H_{13}N$ 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. $C_{26}H_{17}N$ 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. $C_{26}H_{15}AsClN$ 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. $C_{26}H_{15}NS$ 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]*fluoren*[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. $C_{27}H_{15}N$ 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. $C_{33}H_{18}N_4O_7$ 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]*acenaphthyleno*[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 H_2SO_4 was deep violet.

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

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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%).

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