176. *Carcinogenic Nitrogen Compounds. Part XXXV.*[1] *Some Heterocyclic Derivatives of Pyrene.*

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Acridine, phenothiazine, and phenarsazine derivatives, and other nitrogen-containing compounds, bearing a pyrene nucleus, have been synthesised from 1-amino- and 1-hydroxy-pyrene.

Many polycyclic hydrocarbons containing a pyrene nucleus, as, for instance, the mono-, di-, and tri-benzopyrenes, exhibit carcinogenic activity; even in structures unfavourable for carcinogenicity, active hydrocarbons can be obtained by the inclusion of a pyrene group; *e.g.*, although naphthacene is inactive, naphtho[2,1,8-*qra*]naphthacene is active.[2] Hence it was of interest to investigate a number of hitherto unknown nitrogen-containing heterocycles containing pyrene systems.

A convenient intermediate for such compounds was 1-aminopyrene, which is readily prepared by reduction of 1-nitropyrene (I.U.P.A.C. numbering) with hydrazine hydrate in the presence of Raney nickel.[3] The Ullmann–Fetvadjian acridine synthesis,[4] applied to 1-aminopyrene, α-naphthol, and paraformaldehyde, furnished benzo[*a*]phenaleno-[1,9-*ij*]acridine (I); with β-naphthol, the isomer (III) was obtained. Both compounds had the typical orange-yellow colour of naphthacene derivatives, and closely resembled each other in their ultraviolet spectra (Figs. 1 and 2) and other physical properties; their picrates, however, had notably different m. p.s. *meso*-Substituted methyl homologues (II) and (IV) of these acridines were prepared by Bernthsen reactions with acetic anhydride and the corresponding 1-naphthylaminopyrenes, these being readily obtained by iodine-catalysed reaction of 1-aminopyrene with α- and β-naphthol. The ultraviolet absorption spectrum of the 7-methyl derivative (II) (Fig. 2) shows the marked increase of absorption in some bands brought about by *meso*-methylation, reminiscent of previous observations on the *meso*-methylation of anthanthrene.[5]

Both 1-naphthylaminopyrenes readily condensed with arsenic trichloride, to give the corresponding heptacyclic phenarsazine derivatives (V) and (VI). Iodine-catalysed

[1] Part XXXIV, Buu-Hoï and Saint-Ruf, *J.*, 1962, 2630.
[2] Lacassagne, Buu-Hoï, and Zajdela, *Compt. rend.*, 1960, **250**, 3457.
[3] Mabille and Buu-Hoï, *J.*, 1961, 4911.
[4] Ullmann and Fetvadjian, *Ber.*, 1903, **36**, 1029; Buu-Hoï *et al.*, *J.*, 1950, 1146; 1962, 1126.
[5] Buu-Hoï and Lavit, *Bull. Soc. chim. France*, 1958, 1404.

condensation of the naphthylaminopyrenes with sulphur furnished the heptacyclic derivatives of phenothiazine (VII) and (VIII).

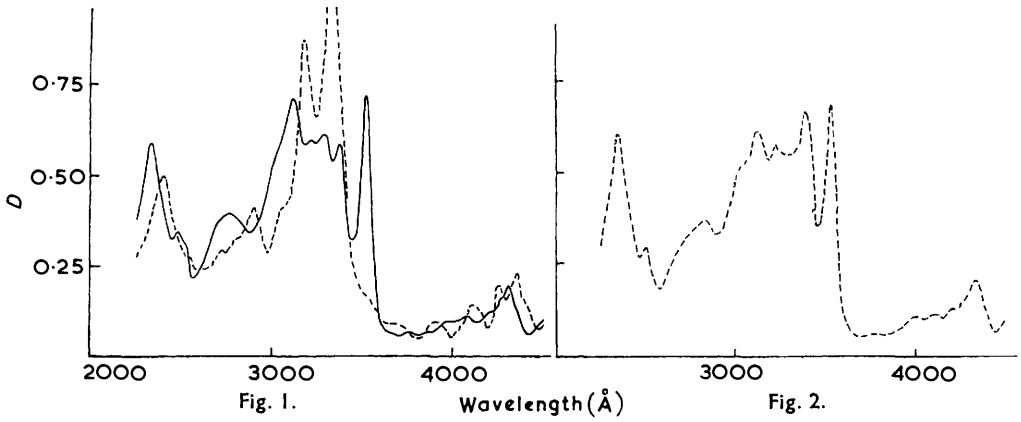
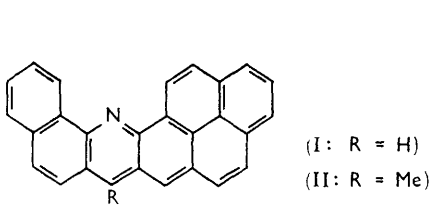


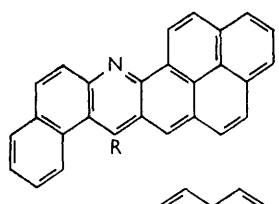
Fig. 1. Fig. 2.

Ultraviolet spectra of (FIG. 1) compounds (I) (——) and (II) (– – –), and (FIG. 2) compound (III). The incomplete portion of the curve for compound (II) has D 1·495 at 3325 Å (max.).

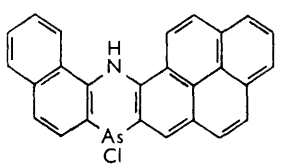
The pyrenoisatin (IX) was synthesised from 1-aminopyrene and diethyl oxomalonate by the Martinet reaction; [6] with *o*-phenylenediamine, it gave the heptacyclic indoloquinoxaline derivative (X). However, 1-aminopyrene did not undergo the Beyer–Combes reaction with pentane-2,4-dione because the intermediate was sulphonated on attempted



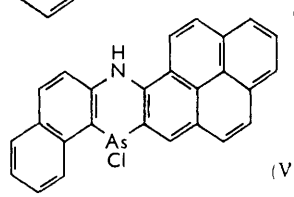
(I: R = H)
(II: R = Me)



(III: R = H)
(IV: R = Me)



(V)



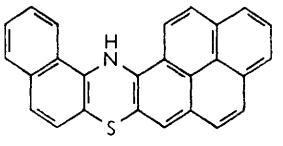
(VI)

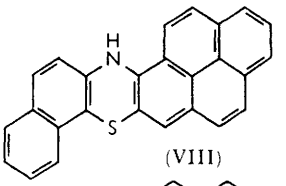
cyclisation with sulphuric acid, and, with phosphorus pentoxide, was recovered unchanged. The compound (XI) was, however, prepared by distillation from zinc of the 7-hydroxy-derivative obtained from 1-aminopyrene and ethyl acetoacetate by the Conrad–Limpach reaction.[7] An " open " nitrogenous derivative of pyrene (XII) was prepared by condensation of β-diethylaminoethyl chloride with 1-hydroxypyrene.

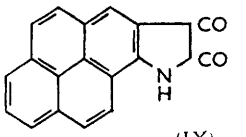
In view of the known carcinogenic activity of 1-acetamidopyrene,[8] several less easily hydrolysed new amides and sulphonamides of 1-aminopyrene were synthesised for testing.

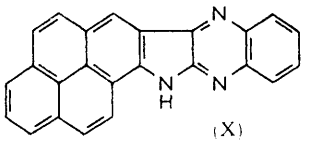
Biological evaluation of the various compounds as carcinogens is being performed by Dr. F. Zajdela and results will be reported elsewhere.

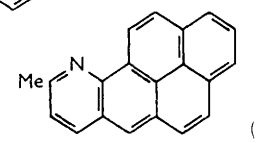
[6] Martinet, *Ann. Chim.* (*France*), 1919, **11**, 15.
[7] Weizmann and Bograchov, *J.*, 1942, 377.
[8] Oiller, Sandin, Miller, and Rusch, *Cancer Res.*, 1955, **15**, 188.

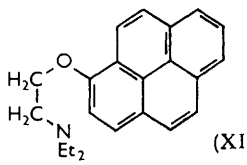

(VII)


(VIII)


(IX)


(X)


(XI)


(XII)

Experimental

M. p.s were taken on a Maquenne bloc.

Preparation of 1-*Aminopyrene*.—Reduction of 1-nitropyrene by iron filings and acetic acid, as described by Vollmann *et al.*,[9] gave 1-aminopyrene in only 63% yield, whereas the following procedure furnished an almost theoretical yield. To a solution of 1-nitropyrene, m. p. 155° (12 g.), and 98% hydrazine hydrate (20 c.c.) in 3 : 1 ethanol–benzene (500 c.c.), Raney nickel (3 g.) was added in small portions, and the mixture was refluxed for 2 hr. Hydrazine hydrate (5 c.c.) and Raney nickel (1 g.) were then added, and heating continued for a further 30 min. The nickel was then filtered off, the solvent distilled off, and the residue crystallised from cyclohexane, to give pale yellow leaflets, m. p. 117°.

The N-*benzenesulphonyl derivative*, prepared in pyridine, formed colourless needles, m. p. 246°, from ethanol (Found: C, 73·8; H, 4·3; N, 3·8. $C_{22}H_{15}NO_2S$ requires C, 73·9; H, 4·2; N, 3·9%). The N-*toluene*-p-*sulphonyl derivative*, needles, m. p. 206° (from ethanol) (Found: C, 74·4; H, 4·6; N, 3·7. $C_{23}H_{17}NO_2S$ requires C, 74·4; H, 4·6; N, 3·8%), and the N-p-*acetamidobenzenesulphonyl derivative*, prisms (1·8 g.), m. p. 275° (from ethanol–benzene) (Found: C, 69·3; H, 4·4. $C_{24}H_{18}N_2O_3S$ requires C, 69·6; H, 4·4%) were similarly prepared; the latter, on deacetylation with sodium hydroxide, gave 1-*sulphanilamidopyrene* as needles, m. p. 252° (from propan-2-ol) (Found: C, 71·2; H, 4·4; N, 7·4. $C_{22}H_{16}N_2O_2S$ requires C, 71·0; H, 4·3; N, 7·5%).

N-1′-*Pyrenylphthalimide*, prepared by refluxing for a few min. a solution of 1-aminopyrene (0·8 g.) and phthalic anhydride (0·6 g.) in acetic acid (30 c.c.), formed yellowish, sublimable prisms (1·2 g.), m. p. 282°, from acetic acid (Found: N, 4·1. $C_{24}H_{13}NO_2$ requires N, 4·0%); *tetrachloro*-N-1′-*pyrenylphthalimide* crystallised from chlorobenzene as lemon-yellow prisms or orange needles, m. p. 349° (sublimation >295°) (Found: C, 59·9; H, 2·1; N, 2·8. $C_{24}H_9Cl_4NO_2$ requires C, 59·6; H, 1·9; N, 2·9%).

Benzo[a]*phenaleno*[1,9-ij]*acridine* (I).—To a boiling mixture of 1-aminopyrene (5 g.) and α-naphthol (4·3 g.), paraformaldehyde (2 g.) was added in small potions; when the violent reaction had subsided, boiling was continued for a few minutes, and the product then fractionated *in vacuo*. The portion of b. p. 310—325°/2 mm. was dissolved in toluene and treated with picric acid, giving a *picrate*, which crystallised from toluene as brown-red needles, decomposing above 152° and melting at 182° on the Maquenne bloc (Found: C, 68·0; H, 3·2; N, 9·8. $C_{33}H_{18}N_4O_7$ requires C, 68·0; H, 3·1; N, 9·6%). Basification with aqueous ammonia gave the *base* (I), crystallising as orange prisms, m. p. 283—284°, from xylene (yield, 15%) and giving in sulphuric acid a brown solution that became dark red (Found: C, 91·3; H, 4·5; N, 3·8. $C_{27}H_{15}N$ requires C, 91·8; H, 4·2; N, 4·0%).

Benzo[c]*phenaleno*[1,9-ij]*acridine* (III).—The reaction was performed as above, but with β-naphthol, and the portion of b. p. 310—325°/2 mm. obtained on fractionation *in vacuo* was converted into a *picrate*, which crystallised from dioxan as reddish-brown prisms, m. p. 281° (decomp. >225°) (Found: C, 68·1; H, 3·4%). The free *base* formed orange needles (19%), m. p. 277—278°, from toluene, giving a brown-red colour in sulphuric acid (Found: C, 91·7; H, 4·4; N, 4·2%). The mixture of compounds (III) and (I) showed a strong depression in the m. p. The absorption spectra shown in the Figures were measured on saturated solutions in ethanol.

[9] Vollmann, Becker, Corell, and Streek, *Annalen*, 1937, **531**, 1.

1-1′-*Naphthylaminopyrene*.—A mixture of 1-aminopyrene (20 g.), α-naphthol (17·8 g.), and iodine (0·5 g.) was heated at 250° for 36 hr.; after cooling, the product was treated with dilute aqueous sodium hydroxide, the secondary *amine* taken up in benzene, the benzene solution washed with water and dried (Na_2SO_4), the solvent evaporated, and the residue fractionated *in vacuo*. The portion of b. p. 310—312°/2 mm. crystallised from ethanol–benzene as greenish-yellow needles (12 g.), m. p. 187—188°, whose solutions showed an intense violet fluorescence (Found: N, 4·1. $C_{26}H_{17}N$ requires N, 4·1%); the corresponding *picrate* formed brownish prisms, m. p. 171—172°, from benzene (Found: N, 9·8. $C_{32}H_{20}N_4O_7$ requires N, 9·8%).

1-2′-*Naphthylaminopyrene*.—Similarly prepared from β-naphthol, this *amine* (12 g.) formed yellow leaflets, m. p. 200—201° (from benzene) (Found: N, 4·4%), whose solutions showed a strong violet fluorescence; it gave a picrate, brown needles, m. p. 182—183° (from benzene). A by-product of this preparation was di-β-naphthylamine, m. p. 171°.

7-*Methylbenzo*[a]*phenaleno*[1,9-ij]*acridine* (II).—A mixture of 1-1′-naphthylaminopyrene (6·5 g.), anhydrous zinc chloride (3 g.), and acetic anhydride (4 g.) was gently refluxed for 24 hr. After cooling, the product was treated with 20% aqueous sodium hydroxide in the presence of hot benzene, the benzene layer dried (Na_2SO_4), the solvent distilled off, and the residue fractionated *in vacuo*. The portion of b. p. 325—335°/2 mm. was dissolved in benzene and converted into a *dipicrate*, crystallising as brick-red needles, m. p. 195° (decomp. >180°), from toluene (Found: N, 11·8. $C_{40}H_{23}N_7O_{14}$ requires N, 11·9%). Treatment with aqueous ammonia afforded the *base* (II), which crystallised as orange prisms (0·7 g.), m. p. 270°, from benzene; its solutions in hydrocarbons showed an intense greenish-yellow fluorescence (Found: C, 91·1; H, 4·7; N, 3·9. $C_{28}H_{17}N$ requires C, 91·5; H, 4·6; N, 3·8%).

7-*Methylbenzo*[c]*phenaleno*[1,9-ij]*acridine* (IV).—Similarly prepared from 1-2′-naphthylaminopyrene, this *base* crystallised as orange needles (0·5 g.), m. p. 272°, from benzene, whose solution in sulphuric acid was brown-red (Found: C, 91·2; H, 4·8; N, 4·0%). The *picrate* formed red needles, m. p. 286° (decomp. >245°), from xylene (Found: N, 10·0. $C_{34}H_{20}N_4O_7$ requires N, 9·4%).

7-*Chloro*-7,14-*dihydrobenzo*[h]*phenaleno*[1,9-bc]*phenarsazine* (V).—A solution of 1-1′-naphthylaminopyrene (2 g.) and arsenic trichloride (1·5 g.) in *o*-dichlorobenzene (10 c.c.) was refluxed for 3 hr. The precipitate obtained on cooling crystallised from *o*-dichlorobenzene as orange prisms (1·5 g.). This *compound* gave unsatisfactory carbon determinations (Found: H, 3·2; N, 3·2. $C_{26}H_{15}AsClN$ requires H, 3·3; N, 3·1%).

7-*Chloro*-7,14-*dihydrobenzo*[a]*phenaleno*[1,9-hi]*phenarsazine* (VI).—Prepared as above, from 1-2′-naphthylaminopyrene, this *compound* formed orange needles, m. p. 321—322°, from *o*-dichlorobenzene (pink halochromy in sulphuric acid becoming violet) (Found: C, 69·2; H, 3·2; N, 2·9. $C_{26}H_{15}AsClN$ requires C, 69·1; H, 3·3; N, 3·1%).

Benzo[j]*phenaleno*[1,9-ab]*phenothiazine* (VII).—A mixture of 1-1′-naphthylaminopyrene (3 g.), sulphur (0·6 g.), and iodine (0·1 g.) was heated for 10 min. at 180—190°, and after cooling, the solid product was recrystallised from toluene, giving deep yellow needles (1·8 g.), m. p. 270° (decomp. >210°); this *compound* gave an indigo-blue colour in sulphuric acid, becoming first violet, then green (Found: C, 83·9; H, 4·2; N, 3·6. $C_{26}H_{15}NS$ requires C, 83·6; H, 4·0; N, 3·7%).

Benzo[h]*phenaleno*[1,9-ab]*phenothiazine* (VIII).—Prepared from 1-2′-naphthylaminopyrene, this *thiazine* formed dark yellow leaflets, m. p. 290° (decomp. >260°), from toluene (Found: C, 83·7; H, 4·1; N, 3·8%).

7,8-*Dihydro*-7,8-*dioxophenaleno*[1,9-fg]*indole* (IX).—Diethyl mesoxalate (5 g.) and 1-aminopyrene (6 g.) were refluxed in acetic acid (70 c.c.) for 1 hr.; the precipitate obtained on dilution with water was collected, washed with water, and heated with 4% aqueous potassium hydroxide for 30 min. in the air. After filtration, the cooled filtrate was acidified with aqueous hydrochloric acid and the precipitate was recrystallised from acetic acid, giving dark violet prisms (0·5 g.), m. p. 290—291° (decomp. >258°) (Found: N, 4·8. $C_{18}H_{19}NO_2$ requires N, 5·1%); this *compound*, like other polycyclic isatins,[10] failed to give the indophenine colour reaction with thiophen. 13*H*-*Phenaleno*[1′,9′a,9′:5,6,7]*indolo*[2,3-b]*quinoxaline* (X), obtained by condensing compound (IX) with *o*-phenylenediamine, formed orange needles, m. p. >370°, from acetic acid (blood-red halochromy in sulphuric acid) (Found: C, 83·7; H, 4·0. $C_{24}H_{13}N_3$ requires C, 84·0; H, 3·8%).

[10] Buu-Hoï and Hiong-Ki-Wei, *Rev. Sci.*, 1944, **82**, 168, 370.

2,5-*Dimethyl*-1-1′-*pyrenylpyrrole*.—Prepared by refluxing for 10 min. a mixture of 1-aminopyrene (1 g.) and hexane-2,5-dione (1·5 g.) with one drop of acetic acid, this *pyrrole* formed colourless needles (1·2 g.), m. p. 147°, from ethanol (Found: C, 89·4; H, 5·8; N, 5·0. $C_{27}H_{17}N$ requires C, 89·5; H, 5·8; N, 4·7%).

Condensation of 1-aminopyrene with pentane-2,4-dione readily yielded 4-1′-*pyrenyliminopentan*-2-*one*, yellow needles, m. p. 152—153° (from ethanol) (Found: N, 4·9. $C_{21}H_{17}NO$ requires N, 4·7%), that could not be cyclised.

9-*Methylphenaleno*[1,9-gh]*quinoline* (XI).—The Conrad–Limpach reaction of 1-aminopyrene (3 g.) and ethyl acetoacetate (3·5 g.) in the presence of piperidine (1 drop) was performed in ethanol (20 c.c.), the mixture being refluxed for 24 hr. The product (3·2 g.) melted at 134° (lit.,[7] m. p. 129°); its cyclisation was effected as in the literature, giving a compound, m. p. 350° (lit.,[7] 350°), which was distilled with zinc powder (10 parts). The distillate was converted into a *picrate*, crystallising as orange needles, m. p. 255°, from toluene (Found: N, 11·2. $C_{26}H_{16}N_4O_7$ requires N, 11·3%). Treatment with aqueous ammonia afforded the free *base*, yellowish needles (10% yield), m. p. 135—136° (from propan-2-ol) (orange colour in sulphuric acid) (Found: C, 89·5; H, 4·7; N, 5·5. $C_{20}H_{13}N$ requires C, 89·9; H, 4·9; N, 5·2%).

1-2′-*Diethylaminoethoxypyrene* (XII).—A solution of 1-hydroxypyrene (22 g.) and sodium hydroxide (4 g.) in ethanol (100 c.c.) was stirred for 1 hr. at 60° with 2-diethylaminoethyl chloride (13 g.), the ethanol was then distilled off, the residue treated with water and chloroform, the chloroform layer dried (Na_2SO_4), the solvent removed, and the residue fractionated *in vacuo*. The ether (20 g.) was a yellow resin, b. p. 220—225°/0·5 mm., whose *picrate* formed orange-yellow prisms, m. p. 185°, from toluene (Found: C, 61·3; H, 4·8; N, 10·4. $C_{28}H_{26}N_4O_8$ requires C, 61·5; H, 4·8; N, 10·3%).

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