874. *Carcinogenic Nitrogen Compounds. Part XXVI.*[1] *Nitrogen-heterocyclic Compounds Derived from Some Polycyclic Arylamines.*

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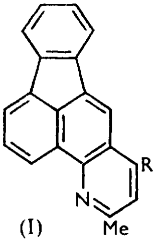
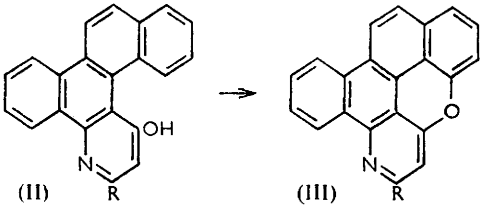
Various cyclisations leading to new nitrogen-heterocyclic systems have been successfully performed with a number of polycyclic arylamines, including 2-aminoanthracene, 3-aminofluoranthene, and 6-aminochrysene; carbostyrils from Conrad–Limpach reactions with 6-aminochrysene give, on zinc dust distillation, always a 4 : 4′-oxygen-bridged compound.

For studies of the relations between constitution and carcinogenic and/or carcinostatic activity in polycyclic compounds, condensed nitrogen-heterocyclic compounds have been prepared, starting from arylamines which have activity of these types, *viz.*: 3-aminofluoranthene and 2-aminoanthracene, which are carcinogenic,[2] and 6-aminochrysene, which possesses antitumour activity.[3]



(I)



(II) (III)

In the fluoranthene series, the product of the Conrad–Limpach condensation of ethyl acetoacetate with 3-aminofluoranthene[1] was readily converted by zinc dust distillation into 6′-methylpyrido(2′ : 3′-3 : 2)fluoranthene (I; $R = H$); a homologue (I; $R = Me$) was obtained by a modified Combes cyclisation[4] of the product of the reaction of acetylacetone with 3-aminofluoranthene. (Incidentally in the preparation of the intermediate 3-nitrofluoranthene,[5] a considerable amount of a dinitrofluoranthene was obtained.) 6-Aminochrysene readily underwent a Conrad–Limpach reaction with ethyl butyryl- or benzoyl-acetate, to give the carbostyrils (II), but these furnished, on zinc dust distillation, 4 : 4′-epoxy-6′-propyl- (III; $R = Pr$) and 4 : 4′-epoxy-6′-phenyl-pyrido(3′ : 2′-5 : 6)-chrysene (III; $R = Ph$), in place of the oxygen-free bases.

2-Aminoanthracene readily underwent a Martinet isatin synthesis[6] with ethyl oxomalonate, to give the derivative (IV), and condensation with *o*-phenylenediamine gave the hexacyclic compound (V). Other cyclisations were also successful; thus, 2-(2-naphthylamino)anthracene, prepared by a Knoevenagel reaction[7] of 2-aminoanthracene with β-naphthol, with arsenic trichloride gave the phenarsazine (VI); and a phenothiazine

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[1] Part XXV, Barrett and Buu-Hoï, *J.*, 1958, 2946.

[2] Schinz, Fritz-Niggli, Campbell, and Schmid, *Oncologia*, 1955, **8**, 233.

[3] Rudali, Buu-Hoï, and Lacassagne, *Compt. rend.*, 1953, **236**, 2020.

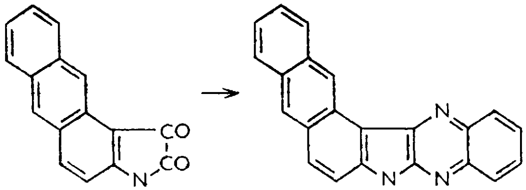
[4] Combes, *Compt. rend.*, 1888, **106**, 1536; Buu-Hoï and Guettier, *ibid.*, 1945, **222**, 665; *Rec. Trav. chim.*, 1946, **65**, 502.

[5] Cf. von Braun and Manz, *Annalen*, 1932, **496**, 170.

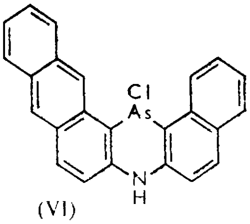
[6] Martinet, *Ann. Chim.*, 1919, **11**, 15; Buu-Hoï and Hiong-Ki-Wei, *Rev. sci.*, 1944, **82**, 168, 306, 370.

[7] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 17; Buu-Hoï, *J.*, 1952, 4346.

compound was obtained by condensation with sulphur, although it was not obtained pure. Condensation of 2-aminoanthracene with hexane-2 : 5-dione led to the anthrylpyrrole (VII); with pentane-2 : 4-dione, a monoanil was obtained, but an attempt to cyclise it with sulphuric acid resulted in sulphonation.

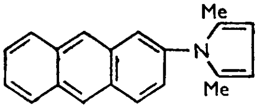


(IV) (V)

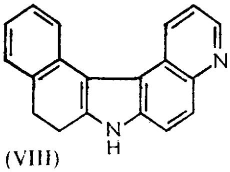


(VI)

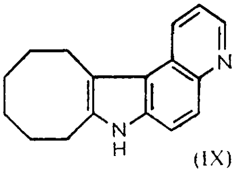
In view of the known carcinogenic [8] and carcinostatic properties [9] of : 4-5 : 6-dibenzocarbazole, the similarly built 6 : 7-dihydro-8 : 9-benzopyrido(3′ : 2′-1 : 2)carbazole (VIII) was prepared by a Fischer indolisation of β-tetralone 6-quinolylhydrazone; [10] *cyclo*octanone 6-quinolylhydrazone similarly gave the indole (IX). This type of compound tends to give very erratic carbon values on analysis.



(VII)



(VIII)



(IX)

EXPERIMENTAL

x : 3-*Dinitrofluoranthene*.—Fluoranthene was nitrated at 75—80° in acetic acid, as in the method of Garascia, Fries, and Ching; [11] a 77% yield of 3-nitrofluoranthene was obtained,

[redacted]

distillate was recrystallised several times from ethanol–benzene, giving yellow needles (0·2 g.), m. p. 191° (Found: C, 85·6; H, 5·2. $C_{24}H_{17}ON$ requires C, 85·9; H, 5·1%); the *epoxy-compound* gave a *picrate* as ochre-yellow needles, m. p. 197° (Found: N, 10·0. $C_{30}H_{20}O_8N_4$ requires N, 9·9%).

4 : 4′-*Epoxy*-6′-*phenylpyrido*(3′ : 2′-5 : 6)*chrysene* (III; R = Ph).—6-Aminochrysene (2 g.) and ethyl benzoylacetate (2 g.) was heated at 200° for 20 min., nitrobenzene (5 c.c.) was added to the semi-solid mass, and the mixture was refluxed for a further 30 min. The crude yellow carbostyril (1·5 g.) thus obtained was collected, washed with acetone, dried, and distilled with zinc powder in the usual way. The distilled *product* crystallised as yellow prisms, m. p. 228—229°, from ethanol–benzene (Found: C, 87·5; H, 4·1. $C_{27}H_{15}ON$ requires C, 87·8; H, 4·1%); the picrate formed orange-yellow needles, m. p. 198°, from ethanol–benzene.

4 : 5-*Dihydro*-4 : 5-*dioxoanthra*[2′ : 1′-2 : 3]*pyrrole* (IV).—2-Aminoanthracene was prepared by reduction of 2-aminoanthraquinone (50 g.) with zinc powder (80 g.) and 5% aqueous sodium hydroxide (2 l.); it formed yellow leaflets, m. p. 241° (lit.,[12] 238°), from toluene. 2-Aminoanthracene (1 g.) and ethyl oxomalonate (2 g.) in acetic acid (10 c.c.) were refluxed for 30 min., then poured into water; the crude precipitate was dissolved in 10% aqueous potassium hydroxide, and the solution was boiled for a few minutes, and, on cooling, acidified with hydrochloric acid. The *compound* (IV) formed violet-red needles, m. p. 228—229°, from acetic acid (Found: C, 77·4; H, 3·4. $C_{16}H_9O_2N$ requires C, 77·7; H, 3·5%). When heated with *o*-phenylenediamine (1 g.) in boiling acetic acid (50 c.c.), it (2 g.) gave *anthra*(2″ : 1″-1′ : 2′)*pyrrolo*(4′ : 5′-2 : 3)*pyrazine* (V), crystallising from pyridine as brick-red leaflets, m. p. >340°, giving a dark violet halochromy in sulphuric acid (Found: N, 12·8. $C_{22}H_{13}N_3$ requires N, 13·1%).

1-2′-*Anthryl*-2 : 5-*dimethylpyrrole* (VII).—2-Aminoanthracene (2 g.), hexane-2 : 5-dione (5 c.c.), and acetic acid (2 c.c.) were refluxed for 5 hr., and the solid precipitate formed on cooling was collected and recrystallised from acetic acid, giving yellowish prisms, m. p. 160° (Found: C, 88·3; H, 6·1. $C_{20}H_{17}N$ requires C, 88·6; H, 6·3%). Pentane-2 : 4-dione (5 c.c.) with 2-aminoanthracene (2 g.) gave, in similar conditions, *pentane*-2 : 4-*dione monoanil* (2 g.), crystallising as yellow prisms, m. p. 196°, from ethanol (Found: C, 82·7; H, 6·5; N, 5·0. $C_{19}H_{17}ON$ requires C, 82·9; H, 6·2; N, 5·0%); an attempt to cyclise this anil with hot sulphuric acid gave only sulphonated resins.

2-2′-*Naphthylaminoanthracene*.—2-Aminoanthracene (2 g.) and β-naphthol (10 g.) were heated with iodine (0·05 g.) for 6 hr. at 200°; after cooling, the solid was pulverised and treated with aqueous sodium hydroxide, and the secondary amine was taken up in benzene and purified by distillation (b. p. ~290°/1 mm.); crystallisation of the distilled *amine* (2 g.) from ethanol gave yellow prisms, m. p. 136—137° (Found: N, 4·4. $C_{24}H_{17}N$ requires N, 4·4%). The *picrate* formed violet needles, m. p. 161°, from benzene (Found: N, 10·5. $C_{30}H_{20}O_7N_4$ requires N, 10·2%).

10-*Chloro*-5 : 10-*dihydro*-1 : 2-*benzonaphtho*(2′ : 3′-8 : 9)*phenarsazine* (VI).—A solution of 2-2′-naphthylaminoanthracene (1 g.) and arsenic trichloride (0·5 g.) in *o*-dichlorobenzene (10 c.c.) was refluxed for 36 hr., then cooled; the precipitate (1 g.) was collected and recrystallised from toluene, to give deep yellow needles of the *phenarsazine*, m. p. 304—305° (decomp. from 290°), giving a violet-red halochromy in sulphuric acid (Found: C, 67·5; H, 3·6. $C_{24}H_{15}NClAs$ requires C, 67·4; H, 3·5%). Condensation of the same secondary amine (1 g.) with sulphur (0·2 g.) in *o*-dichlorobenzene (10 c.c.) in the presence of iodine yielded a thiazine, giving a deep violet halochromy in sulphuric acid.

3 : 4-*Dihydro*-1 : 2-*benzopyrido*(2′ : 3′-8 : 9)*carbazole* (VIII).—6-Quinolylhydrazine dihydrochloride (8 g.), prepared from 6-aminoquinoline according to Wieland and Horner's method,[13] was heated with 2-tetralone (5 g.) and sodium acetate (5 g.) in 30% aqueous ethanol (80 c.c.), and the crude hydrazone was indolised with sulphuric acid (3 c.c.) and acetic acid (20 c.c.) at 100° for 10 min. The *carbazole* (3·5 g.) obtained on basification was crystallised several times from ethanol–acetone, giving yellowish leaflets, m. p. 263° (Found: C, 84·0; H, 5·5; N, 10·0. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2; N, 10·3%). The picrate crystallised as red leaflets, m. p. 298°, from nitrobenzene.

2 : 3-cyclo*Octenopyrido*(3′ : 2′-4 : 5)*indole* (IX).—Prepared as above, from *cyclo*octanone (2·5 g.) and 6-quinolylhydrazine dihydrochloride (2·1 g.), this *indole* (2 g.) formed pale yellow

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[12] Ruggli and Henze, *Helv. Chim. Acta*, 1930, **13**, 409.

[13] Wieland and Horner, *Annalen*, 1938, **536**, 89.

needles, m. p. 214° from ethanol (Found: N, 11·2. $C_{17}H_{18}N_2$ requires N, 11·2%); the picrate formed orange needles, m. p. 274°, from ethanol.

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