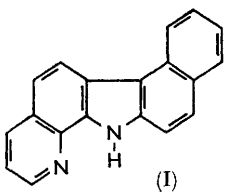
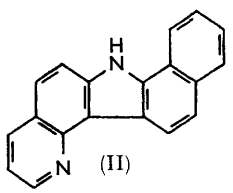
28. *Carcinogenic Nitrogen Compounds. Part XXXII.*[1] *The Synthesis of New Highly Active Benzopyridocarbazoles.*

By N. P. Buu-Hoï, F. Périn, and P. Jacquignon.

The synthesis is described of a new series of benzopyridocarbazoles and related compounds, some of which display high carcinogenic activity. An isomer effect was noted in the indolisation of the various quinolylhydrazones investigated.

Benzopyridocarbazoles, which in theory are derived from the corresponding dibenzocarbazoles by aza-substitution, were recently synthesised [2] for evaluation of their carcinogenic activity and some of them, as for instance 5,6-benzopyrido(2',3':1,2)carbazole (I), showed a sarcomogenic potency even greater than that of the parent dibenzocarbazole; further, the action of compound (I) differs according to the sex of the animal (mouse), the male being considerably the more susceptible.[3] These reasons prompted investigation of the influence of the site occupied by the pyridine-nitrogen atom.


(I)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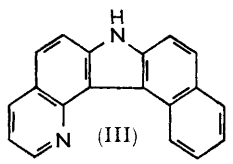
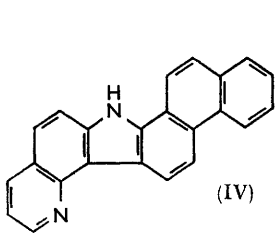
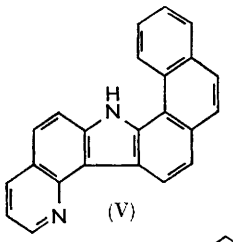

(III)

Synthesis of compounds of this type involves indolisation of quinolylhydrazones of α- and β-tetralone, and the behaviour of 3-, 5-, 7-, and 8-quinolylhydrazones and of 2-methyl-8-quinolylhydrazones has been investigated. The 7-quinolylhydrazones of α- and β-tetralone were readily indolised by sulphuric and acetic acid to the corresponding dihydrocarbazoles, which were dehydrogenated with palladium–charcoal to compounds (II) and (III); similarly the carbazoles (IV) and (V) were prepared from the 7-quinolylhydrazones of 1,2,3,4-tetrahydro-1- and -4-oxophenanthrene. However, α-tetralone 8-quinolyl- and 2-methyl-8-quinolyl-hydrazone were cyclised only by heating with anhydrous zinc chloride, which caused dehydrogenation of the intermediary dihydrocarbazoles, compounds (VI) and (VII) being thus directly obtained; the same method of cyclisation, applied to the 8-quinolylhydrazones of 1,2,3,4-tetrahydro-1- and -4-oxophenanthrene, likewise yielded directly the carbazoles (IX) and (X). β-Tetralone 2-methyl-8-quinolylhydrazone, however, was cyclised by the sulphuric–acetic reagent, giving compound (VIII) after dehydrogenation of the intermediate.

The difficulties encountered with 8-quinolylhydrazones could be ascribed to the presence of a *peri*-nitrogen atom, since the isomeric 7-, 6-, and 5-quinolylhydrazones all underwent indolisation under the influence of the sulphuric–acetic acid mixture. The 5-quinolylhydrazones are particularly reactive, as partial cyclisation occurred already during their

[1] Part XXXI, Buu-Hoï, Jacquignon, and Allegrini, *J.*, 1961, 4836.
[2] Buu-Hoï, Périn, and Jacquignon, *J.*, 1960, 4500.
[3] Lacassagne, Buu-Hoï, Zajdela, Périn, and Jacquignon, *Nature*, 1961, **191**, 1005.


(IV)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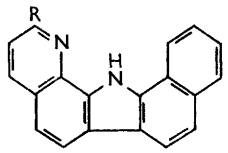
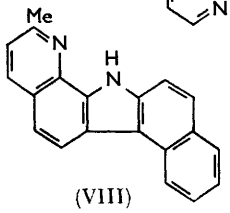
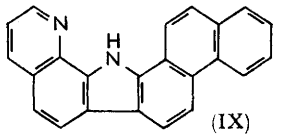
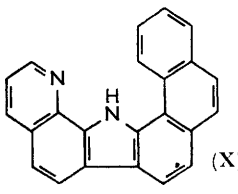
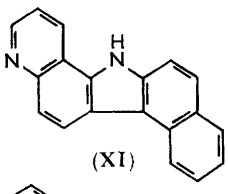

(VI; R = H) (VII; R = Me)

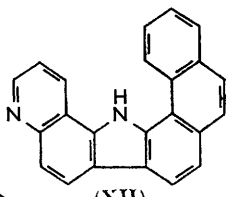

(VIII)


(IX)

preparation from 5-quinolylhydrazine hydrochloride; from β-tetralone and 1,2,3,4-tetrahydro-4-oxophenanthrene, compounds (XI) and (XII) were thus readily prepared.


(X)


(XI)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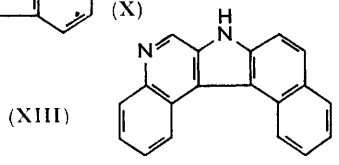
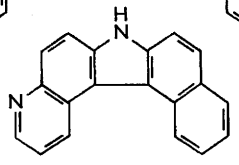
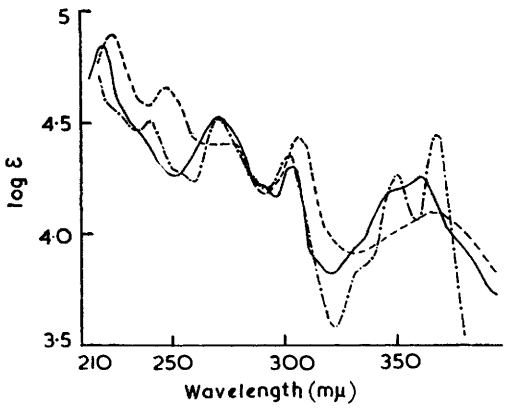

(XIII)


(XIV)

From Clemo and Felton's results [4] it could be inferred that indolisation of 3-quinolylhydrazones would occur at the 4- rather than at the 2-position. This has been confirmed



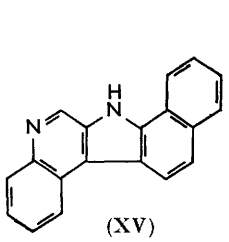
Absorption spectra of (——) compound (XIII), (– – –) compound (XIV), and (— · — ·) 3,4:5,6-dibenzocarbazole.

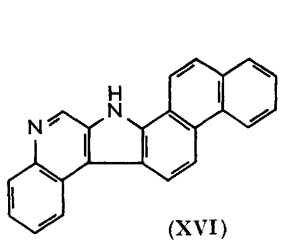
spectroscopically, the dibenzo-β-carboline (XIII) prepared from β-tetralone showing the same main ultraviolet absorption bands as 3,4:5,6-dibenzocarbazole and 3,4-benzopyrido-(3′,2′:5,6)carbazole [2] (XIV) (see Figure).

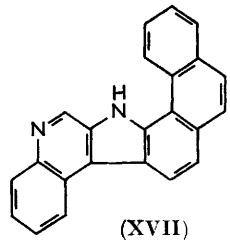
The polycyclic β-carbolines (XV), (XVI), and (XVII) were also prepared from the 3-quinolylhydrazones of α-tetralone and 1,2,3,4-tetrahydro-1- and -4-oxophenanthrene,

[4] Clemo and Felton, *J.*, 1951, 671.

It is to be noted that from the four 3-quinolylhydrazones examined, only that of β-tetralone could be cyclised with the sulphuric–acetic acid mixture.


(XV)


(XVI)


(XVII)

Biological experiments in mice show that several of the benzopyridocarbazoles reported here induce sarcomas by subcutaneous injection, the degree of carcinogenicity depending on the position occupied by the pyridine-nitrogen atom; compound (XI), for instance, ranks among the most potent sarcomogens known, whilst compound (XIV) is only slightly active.* These variations are reminiscent of the difference in carcinogenic activity between 1,2- and 3,4-benzacridine.[5]

Experimental

Preparation of Intermediates.—3-Quinolylhydrazine was prepared from 3-aminoquinoline by the method of Wieland and Horner [6] as modified by Clemo and Swan; [7] the free base, recrystallised from benzene, melted at 180·5° (lit.,[4] m. p. 176—178°); a similar method was used for the synthesis of 5-quinolylhydrazine, m. p. 163° (from benzene) (lit.,[8] m. p. 151°). 7-Nitroquinoline was prepared from *m*-nitroaniline by a Skraup reaction, the product containing 60% of 5-nitroquinoline and 40% of 7-nitroquinoline; 7-aminoquinoline, which served in the preparation of 7-quinolylhydrazine, formed colourless prisms, m. p. 97°, from cyclohexane (lit.,[9] m. p. 94°). The various quinolyl- and 2-methylquinolyl-hydrazones were prepared by refluxing for 1 hr. an aqueous-ethanolic solution of the corresponding quinolylhydrazine hydrochloride and cyclic ketone in the presence of sodium acetate.

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

1,2-*Benzopyrido*(2′,3′:5,6)*carbazole* (II).—*α-Tetralone 7-quinolylhydrazone* formed yellowish needles, m. p. 212°, from ethanol (Found: N, 14·9. $C_{19}H_{17}N_3$ requires N, 14·6%). A mixture of this compound (2 g.) and freshly fused zinc chloride (4 g.) was heated for 45 min. at 280—300°; the cooled dark brown mass was triturated with aqueous sodium chloride, and the solid precipitate was collected, washed with water, and recrystallised from benzene, giving pale yellow needles (0·7 g.), m. p. 229°. Like many substances of the same type, this *compound* gave very poor analyses for carbon (Found: H, 4·7; N, 10·1. $C_{19}H_{12}N_2$ requires H, 4·5; N, 10·4%). Its *picrate* crystallised as orange needles, m. p. 294°, from chlorobenzene (Found: N, 13·9. $C_{25}H_{15}N_5O_7$ requires N, 14·1%).

1,2-*Dihydro*-5,6-*benzopyrido*(2′,3′:3,4)*carbazole*.—β-Tetralone 7-quinolylhydrazone, obtained as an amorphous mass (2 g.), was heated for 10 min. at 100° with acetic acid (5 c.c.) and sulphuric acid (1 c.c.); after cooling and basification with aqueous ammonia, the precipitated *product* was recrystallised from benzene, giving cream-coloured prisms (1 g.), m. p. 222° (Found: C, 84·5; H, 5·3; N, 10·1. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2; N, 10·4%). Its *picrate* formed orange needles, m. p. 257° (decomp. >210°), from ethanol (Found: N, 13·8. $C_{25}H_{17}N_5O_7$ requires N, 14·0%).

5,6-*Benzopyrido*(2′,3′:3,4)*carbazole* (III).—A mixture of the foregoing dihydro-compound (0·5 g.) and 5% palladium–charcoal (0·5 g.) was heated at 310—320°, and the dehydrogenation *product* was sublimed over palladium–charcoal and recrystallised from benzene, giving yellowish needles (0·3 g.), m. p. 244° (Found: C, 84·8; H, 4·1; N, 10·3. $C_{19}H_{12}N_2$ requires C, 85·1;

* The naphthopyridocarbazoles tested are not carcinogenic or only very weakly so.

[5] Cf. Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.
[6] Wieland and Horner, *Annalen*, 1938, **536**, 92.
[7] Clemo and Swan, *J.*, 1945, 867.
[8] Kaufmann and Zeller, *Ber.*, 1917, **50**, 1627.
[9] Hamer, *J.*, 1921, **119**, 1436.

H, 4·5; N, 10·4%). The *picrate* formed orange-red needles, m. p. 232° (decomp. >210°), from ethanol (Found: N, 14·4%).

Naphtho(2′,1′:1,2)*pyrido*(2″,3″:5,6)*carbazole* (IV).—1,2,3,4-*Tetrahydro*-1-*oxophenanthrene* 7-*quinolylhydrazone* formed yellow needles, m. p. 233°, from chlorobenzene (Found: C, 81·9; H, 5·9; N, 12·5. $C_{23}H_{19}N_3$ requires C, 81·9; H, 5·6; N, 12·5%). Cyclisation of this hydrazone (1 g.) with zinc chloride (2 g.) was accompanied by dehydrogenation and led to the *carbazole* (IV), crystallising as cream-coloured, sublimable needles (0·5 g.), m. p. 322°, from toluene; this compound was recovered unchanged on sublimation over palladium–charcoal and gave unsatisfactory carbon analyses (Found: H, 4·3; N, 8·9. $C_{23}H_{14}N_2$ requires H, 4·4; N, 8·8%). The *picrate* formed orange prisms, m. p. 345° (decomp. >270°), from cyclohexanone (Found: N, 13·0. $C_{29}H_{17}N_5O_7$ requires N, 12·8%).

Naphtho(1′,2′:1,2)*pyrido*(2″,3″:5,6)*carbazole* (V).—Prepared by cyclisation of the crude 1,2,3,4-tetrahydro-4-oxophenanthrene 7-quinolylhydrazone by means of zinc chloride, this *carbazole* crystallised as cream-coloured, sublimable needles, m. p. 232°, from benzene (Found: N, 9·1%) [*picrate*, orange-yellow prisms, m. p. 292° (decomp. >240°), from cyclohexanone (Found: N, 12·6%)].

7,8-*Benzopyrido*(3′,2′:1,2)*carbazole* (VI).—α-*Tetralone* 8-*quinolylhydrazone*, lemon-yellow needles, m. p. 210°, from ethanol (Found: N, 14·3%), underwent cyclisation with zinc chloride to the *carbazole* (VI), which crystallised as yellowish needles, m. p. 193°, from benzene (Found: C, 84·7; H, 4·4; N, 10·7. $C_{19}H_{12}N_2$ requires C, 85·1; H, 4·5; N, 10·4%); this compound was recovered unchanged after treatment with palladium–charcoal, and gave a picrate which formed deep yellow prisms, m. p. 286° (decomp. >260°), from benzene.

6″-*Methyl*-7,8-*benzopyrido*(3′,2′:1,2)*carbazole* (VII).—α-Tetralone 8-quinaldylhydrazone, bright yellow leaflets, m. p. 158° (from ethanol–benzene), yielded on treatment with zinc chloride the *carbazole* (VII), crystallising as cream-coloured leaflets, m. p. 192°, from ethanol (Found: N, 9·7. $C_{20}H_{14}N_2$ requires N, 9·9%) [*picrate*, deep yellow prisms, m. p. 299° (decomp. >270°), from ethanol (Found: N, 13·7. $C_{26}H_{17}N_5O_7$ requires N, 13·6%)].

7,8-*Dihydro*-6″-*methyl*-5,6-*benzopyrido*(2′,3′:1,2)*carbazole* was obtained by treatment of the crude β-tetralone 8-quinaldylhydrazone with sulphuric–acetic acid and formed cream-coloured leaflets, m. p. 210°, from ethanol (Found: C, 84·5; H, 5·7; N, 9·9. $C_{20}H_{16}N_2$ requires C, 84·5; H, 5·5; N, 10·0%). Sublimation over palladium–charcoal gave 6″-*methyl*-5,6-*benzopyrido*(2′,3′:1,2)*carbazole* (VIII), crystallising as cream-coloured needles, m. p. 256°, from ethanol (Found: N, 9·8%), and giving a yellow *picrate*, m. p. 345° (decomp. >290°), from ethanol (Found: N, 13·4%).

Naphtho(2′,1′:1,2)*pyrido*(3″,2″:7,8)*carbazole* (IX).—1,2,3,4-*Tetrahydro*-1-*oxophenanthrene* 8-*quinolylhydrazone*, saffron-yellow leaflets, m. p. 151°, from cyclohexane (Found: N, 12·7%), was cyclised with zinc chloride to the *carbazole* (IX), crystallising as cream-coloured needles, m. p. 253°, from chlorobenzene (Found: C, 86·5; H, 4·5. $C_{23}H_{14}N_2$ requires C, 86·8; H, 4·4%) [*picrate*, orange-yellow needles, m. p. 345° (decomp. >280°), from ethanol (Found: N, 12·6%)].

Naphtho(1′,2′:7,8)*pyrido*(3″,2″:1,2)*carbazole* (X).—1,2,3,4-*Tetrahydro*-4-*oxophenanthrene* 8-*quinolylhydrazone*, lemon-yellow needles, m. p. 135°, from cyclohexane (Found: N, 12·8%), underwent similar cyclisation to give the *carbazole* (X), yellowish needles, m. p. 191° (from chlorobenzene) (Found: N, 8·5%) [*picrate*, orange prisms, m. p. 298° (decomp. >270°), from ethanol (Found: N, 12·6%)].

7,8-*Dihydro*-5,6-*benzopyrido*(3′,2′:1,2)*carbazole*, prepared by indolisation with sulphuric–acetic acid of the crude β-tetralone 5-quinolylhydrazone (which already contained some cyclisation product), formed yellowish needles, m. p. 344°, from ethanol (Found: C, 84·1; H, 5·2; N, 10·2%). Its picrate formed deep orange needles, m. p. 282° (decomp. >260°), from ethanol. Sublimation over palladium–charcoal yielded 5,6-*benzopyrido*(3′,2′:1,2)*carbazole* (XI), crystallising as straw-coloured needles, m. p. 368°, from ethanol (Found: C, 85·2; H, 4·5; N, 10·2%) and giving a *picrate*, yellow needles, m. p. 309° (decomp. >280°), from nitrobenzene (Found: N, 14·0%).

5,6-*Dihydronaphtho*(1′,2′:7,8)*pyrido*(2″,3″:1,2)*carbazole*, similarly prepared from the crude 1,2,3,4-tetrahydro-4-oxophenanthrene 5-quinolylhydrazone, formed yellowish needles, m. p. 308°, from benzene (Found: C, 86·3; H, 4·7; N, 8·7. $C_{23}H_{14}N_2$ requires C, 86·8; H, 4·4; N, 8·8%) and gave a *picrate*, orange-yellow needles, m. p. 292° (decomp. >270°), from ethanol (Found: N, 12·6. $C_{29}H_{17}N_5O_7$ requires N, 12·8%). Dehydrogenation gave *naphtho*(1′,2′:7,8)-*pyrido*(2″,3″:1,2)*carbazole* (XII), crystallising as pale yellow needles, m. p. 319°, from toluene

(Found: H, 4·5; N, 8·7%) [*picrate*, yellow prisms, m. p. 327° (decomp. >280°), from ethanol (Found: N, 13·0%)].

1,2:6,7-*Dibenzo*-β-*carboline* (XV).—α-*Tetralone* 3-*quinolylhydrazone* crystallised from benzene–cyclohexane as pale yellow needles, m. p. 182° (Found: C, 79·4; H, 5·8; N, 14·6. $C_{19}H_{17}N_3$ requires C, 79·4; H, 5·9; N, 14·6%). An attempt to cyclise this hydrazone with sulphuric–acetic acid left it unchanged. Treatment with zinc chloride afforded the *carboline* (XV), crystallising as yellowish needles, m. p. 341°, from acetone (Found: C, 84·8; H, 4·6; N, 10·6%). Its *picrate* formed deep yellow prisms, m. p. 298° (decomp. >270°), from ethanol (Found: N, 14·1%).

6,7-*Dihydro*-1,2:8,9-*dibenzo*-β-*carboline*.—Obtained by cyclisation with sulphuric–acetic acid of the crude β-tetralone 3-quinolylhydrazone, this *compound* formed cream-coloured leaflets, m. p. 303°, from ethanol (Found: C, 84·7; H, 5·1; N, 10·4%) and gave a *picrate*, orange prisms, m. p. 313° (decomp. >260°), from ethanol (Found: N, 13·6%). Dehydrogenation over palladium–charcoal furnished 1,2:8,9-*dibenzo*-β-*carboline* (XIII), cream-coloured leaflets, m. p. 320°, from ethanol (Found: C, 84·9; H, 4·7; N, 10·4%) [*picrate*, deep yellow needles, m. p. 280° (decomp. >260°), from ethanol (Found: N, 13·9%)].

1,2-*Benzonaphtho*(1′,2′:6,7)-β-*carboline* (XVI).—1,2,3,4-*Tetrahydro*-1-*oxophenanthrene* 3-*quinolylhydrazone* formed yellow needles, m. p. 251°, from xylene (Found: C, 81·9; H, 5·7; N, 12·5%). Cyclisation, which failed with sulphuric–acetic acid, gave with zinc chloride the *carboline* (XVI), which was poorly soluble in the usual solvents and was purified by sublimation *in vacuo* at 320°, yielding pale yellow prisms, m. p. 366° (Found: H, 4·3; N, 9·0%). Its *picrate* crystallised as orange needles, m. p. 277°, from ethanol (Found: N, 12·9%).

1,2-*Benzonaphtho*(2′,1′:6,7)-β-*carboline* (XVII).—Prepared by cyclisation of the crude 1,2,3,4-tetrahydro-4-oxophenanthrene 3-quinolylhydrazone by means of zinc chloride, this *carboline* formed cream-coloured needles, m. p. 307°, from xylene (Found: C, 87·0; H, 4·4%) [*picrate*, orange-yellow prisms, m. p. 287° (decomp. >270°), from ethanol (Found: N, 12·6%)].

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