870. *Carcinogenic Nitrogen Compounds. Part XXVIII.*[1] *Azadibenzofluorenes and Related Compounds.*

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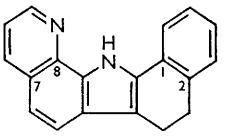
Aza-derivatives of the carcinogenic 1,2:5,6-, 1,2:7,8-, and 3,4:5,6-dibenzocarbazole have been synthesised from α- and β-tetralone with 5-, 6-, and 8-quinolylhydrazine, together with some of their higher polycyclic analogues.

The high incidence of carcinogenicity in the benzacridine and dibenzacridine series shows that the introduction of heterocyclic nitrogen atoms into the molecules of polycyclic hydrocarbons does not suppress, and at times enhances, this type of biologcal activity;[2] further, the carcinogenic potency of compounds such as dinaphthazine[3] and tricycloquinazoline[4] indicates that the presence of several nuclear nitrogen atoms is not necessarily detrimental. These considerations prompted the preparation, for biological investigation, of aza-derivatives of 1,2:5,6-, 1,2:7,8- and 3,4:5,6-dibenzocarbazole, all of which are to some degree carcinogenic.[5] The method used was the Fischer indolisation of quinolylhydrazones of the appropriate polycyclic ketones; several authors had already studied the cyclisation of a number of quinolylhydrazones of cyclohexanone,[6] but similar reactions with α- and β-tetralone had not been reported.

5-, 6-, and 8-Quinolylhydrazine were used for this work, the hydrazones of the 8-isomer being in general the least amenable to cyclisation. Thus, whilst the benzopyridocarbazoles were readily obtained from the 5- and the 6-quinolylhydrazone of α-tetralone, only negative results were recorded with the 8-quinolylhydrazone, even when drastic procedures were applied. This failure is probably connected with the unfavourable steric conditions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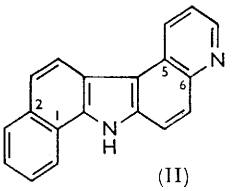
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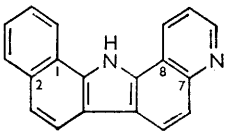
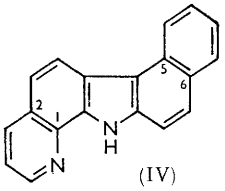

(III)

present in *cis*-bisangular cyclisations in the vicinity of a *peri*-nitrogen atom (cf. I). Indolisation of the 6- and the 8-quinolylhydrazone of β-tetralone yielded dihydrobenzopyridocarbazoles that were smoothly dehydrogenated by means chloranil in xylene[7] or, more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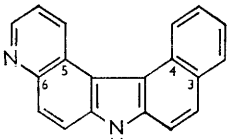
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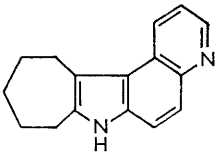

(VI)

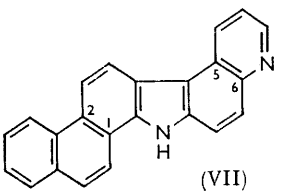
conveniently, by palladium–charcoal, giving compounds (II)—(V). Compound (II) is isosteric with the weakly carcinogenic 1,2:7,8-dibenzocarbazole, (IV) is isosteric with the moderately carcinogenic 1,2:5,6-dibenzocarbazole, and (V) is isosteric with the strong

[1] Part XXVII, Buu-Hoï and Jacquignon, *J.*, 1959, 3095.
[2] Cf. Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.
[3] Hackmann, *Z. Krebsforsch.*, 1951, **58**, 56.
[4] Baldwin, Butler, Cooper, and Partridge, *Nature*, 1958, **181**, 838; Baldwin, Cunningham, and Partridge, *Brit. J. Cancer*, 1959, **13**, 94.
[5] Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429; Boyland and Mawson, *Biochem. J.*, 1938, **32**, 1640; Lacassagne, Buu-Hoï, Zajdela, and Xuong, *Bull. Cancer*, 1955, **42**, 3.
[6] Dewar, *J.*, 1944, 616; Mann, Prior, and Willcox, *J.*, 1959, 3830.
[7] Barclay and Campbell, *J.*, 1945, 530; Buu-Hoï, Hoán, and Khoi, *J. Org. Chem.*, 1949, **14**, 492.

carcingogen 3,4:5,6-dibenzocarbazole. We failed in an attempt to dehydrogenate similarly the cycloheptenopyridoindole (VI) (prepared from cycloheptanone).

The same reactions were applied also to more complex ketones: 1,2,3,4-tetrahydro-1- and -4-oxophenanthrene and 6-quinolylhydrazine readily gave the compounds (VII) and (VIII), and the former ketone with 5-quinolylhydrazine gave compound (IX). But again we failed to indolize the 8-quinolylhydrazones of 1,2,3,4-tetrahydro-1- and -4-oxophenanthrene.

In the case of 6-quinolylhydrazones the orientation postulated for the products is based on the fact [8] that the quinoline nucleus does not react according to formal structures lacking a 5,6-double bond, and on the resemblance of the ultraviolet absorption spectra of compounds (II) and (V) to those of their benzenoid isosters.



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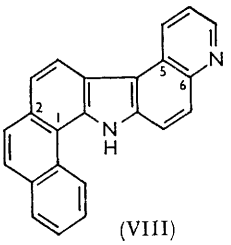
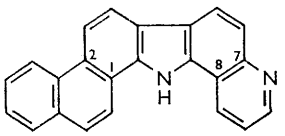


(VIII)



(IX)

Although quinoline derivatives generally fail to give addition compounds with tetrachlorophthalic anhydride,[9] 3,4-dihydronaphtho(2′,1′:1,2)pyrido(3″,2″:5,6)carbazole gave a red molecular complex with this reagent. Biological tests for sarcoma-inducing properties by subcutaneous injection in mice show that compound (V) is active; the aza-substitution has thus not eliminated the carcinogenicity of 3,4:5,6-dibenzocarbazole.

Experimental

Preparation of Intermediates.—6-Quinolylhydrazine hydrochloride was prepared from 6-aminoquinoline by Wieland and Horner's method,[10] and the 5- and the 8-isomer in a similar way; 8-quinolylhydrazine was isolated, on basification of its hydrochloride with aqueous sodium hydroxide, as a pale yellow solid, b. p 188—189°/13 mm., m. p. 65°, sensitive to the air and light, and could be conveniently used in place of its hydrochloride for the formation of hydrazones.

α-*Tetralone 5-Quinolylhydrazone.*—A solution of 5-quinolylhydrazine hydrochloride (1·9 g.) and sodium acetate (1·2 g.) in ethanol (5 c.c.) and water (15 c.c.) was heated for 1 hr. on a water-bath with α-tetralone (1·25 g.); after cooling, the mixture was basified with a few drops of aqueous ammonia, and the precipitated *hydrazone* was collected; it recrystallised from ethanol as bright yellow needles (2 g.), m. p. 234° (Found: C, 79·7; H, 6·2; N, 14·4. $C_{19}H_{17}N_3$ requires C, 79·4; H, 5·9; N, 14·6%).

3,4-*Dihydro*-1,2-*benzopyrido*(2′,3′:7,8)*carbazole.*—The foregoing hydrazone (2 g.) was heated on a water-bath for 10 min. with acetic acid (5 c.c.) and sulphuric acid (1 c.c.); after cooling, the red solution was poured into aqueous ammonia, and the precipitated *dihydrocarbazole* was collected; it recrystallised from ethanol as pale yellow needles (1·5 g.), m. p. 276° (Found: N, 10·0. $C_{19}H_{14}N_2$ requires N, 10·4%); it gave erratic carbon values on combustion. Its *picrate* crystallised as orange-red needles, m. p. 345°, from ethanol (Found: N, 14·3. $C_{25}H_{17}N_5O_7$ requires N, 14·0%).

1,2-*Benzopyrido*(2′,3′:7,8)*carbazole* (III).—A mixture of the foregoing compound (1 g.) and palladium–charcoal (0·5 g.) was heated at 310°, and the sublimate was resublimed over palladium–charcoal. The *carbazole* formed cream-coloured needles (0·6 g.), m. p. 311°, from ethanol (Found: C, 85·2; H, 4·7. $C_{19}H_{12}N_2$ requires C, 85·1; H, 4·5%); the *picrate* formed orange needles, m. p. 335°, from ethanol (Found: N, 13·8. $C_{25}H_{15}N_5O_7$ requires N, 14·1%).

[8] Cf. Marckwald, *Annalen*, 1893, **274**, 331; 1894, **279**, 1; Badger, "Structures and Reactions of the Aromatic Compounds," Cambridge Univ. Press, 1954, p. 156.
[9] Buu-Hoï and Jacquignon, *Bull. Soc. chim. France*, 1957, 488.
[10] Wieland and Horner, *Annalen*, 1958, **536**, 92.

3,4-*Dihydro*-1,2-*benzopyrido*(3′,2′:5,6)*carbazole*.—α-*Tetralone* 6-*quinolylhydrazone*, prepared from 6-quinolylhydrazine hydrochloride, as above, formed yellow needles, m. p. 233°, from ethanol (Found: C, 79·2; H, 6·0; N, 14·5%). Indolisation gave the *dihydrocarbazole*, crystallising as cream-coloured needles (70%), m. p. 276°, from ethanol (Found: N, 10·4%); this compound also gave erratic carbon analyses. Its *picrate* formed red needles, m. p. 295°, from ethanol (Found: N, 13·8%).

1,2-*Benzopyrido*(3′,2′:5,6)*carbazole* (II).—A xylene solution of the above dihydro-compound (1·2 g.) was refluxed for 6 hr. with chloranil (2 g.); the dark precipitate formed on cooling was extracted with aqueous sodium hydroxide, and the undissolved *carbazole* was recrystallised twice from ethanol (charcoal), giving fine cream-coloured needles (0·5 g.), m. p. 325° (decomp. >295°) (Found: N, 10·1%); its orange *picrate* had m. p. >340° (Found: N, 14·0%).

Attempted Preparation of Compound (I) *and its Analogues*.—A solution of 8-quinolylhydrazine (1·5 g.) and α-tetralone (1·25 g.) in ethanol (10 c.c.) was refluxed for 1 hr.; α-*tetralone* 8-*quinolylhydrazone* was precipitated on cooling and recrystallised from ethanol as lemon-yellow needles (1·8 g.), m. p. 210° (Found: C, 79·1; H, 6·2; N, 14·3%). The compound was recovered unchanged after treatment with sulphuric acid (1 vol.) in acetic acid (5 vol.), even after being heated for 30 min.; increase in concentration of sulphuric acid and even longer heating resulted in decomposition of the hydrazone. 1,2,3,4-*Tetrahydro*-1-*oxophenanthrene* 8-*quinolylhydrazone*, prepared from the ketone (1·5 g.) with 8-quinolylhydrazine (1·5 g.) in ethanol (10 c.c.), formed yellow leaflets (2 g.), m. p. 151°, from cyclohexane (Found: C, 82·3; H, 5·9; N, 12·7. $C_{23}H_{19}N_3$ requires C, 81·9; H, 5·6; N, 12·5%). 1,2,3,4-*Tetrahydro*-4-*oxophenanthrene* 8-*quinolylhydrazone* formed lemon yellow needles, m. p. 135°, from cyclohexane (Found: N, 12·8%). These two hydrazones resisted attempts at cyclisation.

3,4-*Benzopyrido*(3′,2′:5,6)*carbazole* (V).—Dehydrogenation of the corresponding dihydrocarbazole [11] was effected with chloranil as above, affording a 50% yield of the *carbazole*, which crystallised as cream-coloured leaflets, m. p. 270°, from ethanol (Found: N, 10·3%); its *picrate* crystallised as orange-yellow needles, m. p. 317°, from ethanol (Found: C, 60·1; H, 2·9. $C_{25}H_{15}N_5O_7$ requires C, 60·4; H, 3·0%).

5,6-*Benzopyrido*(2′,3′:1,2)*carbazole* (IV).—β-*Tetralone* 8-*quinolylhydrazone* formed orange-yellow needles, m. p. 136°, from ethanol (Found: C, 79·1; H, 6·6%); its indolisation, readily effected with the usual sulphuric–acetic acid reagent, furnished 7,8-*dihydro*-5,6-*benzopyrido*-(2′,3′:1,2)*carbazole*, crystallising as cream-coloured needles, m. p. 195°, from cyclohexane (Found: C, 84·5; H, 5·2; N, 10·5%), and giving a *picrate*, orange-yellow prisms (from ethanol), m. p. 312° (Found: N, 14·0%). Dehydrogenation with palladium–charcoal afforded a 70% yield of the *carbazole* as sublimable, colourless needles, m. p. 234° (from benzene) (Found: C, 85·4; H, 4·5; N, 10·3%); the corresponding picrate was bright yellow.

4′,5′-*Cycloheptenopyrrolo*(3′,2′:5,6)*quinoline* (VI).—*Cycloheptanone* 6-*quinolylhydrazone*, prepared from the ketone (1·6 g.) and 6-quinolylhydrazine hydrochloride (3·2 g.) with sodium acetate (2·2 g.) in ethanol, formed yellow needles (2·8 g.), m. p. 168°, from ethanol (Found: N, 16·3. $C_{16}H_{19}N_3$ requires N, 16·6%). Indolisation, effected by heating this compound (2·5 g.) for 1 hr. on a water-bath with a solution of sulphuric acid (3 c.c.) in acetic acid (10 c.c.), gave the *product* (VI), crystallising as yellowish prisms (1·8 g.), m. p. 179°, from light petroleum (Found: C, 81·3; H, 6·5; N, 12·0. $C_{16}H_{16}N_2$ requires C, 81·4; H, 6·8; N, 11·9%). The *picrate* formed orange-yellow prisms, m. p. 266°, from ethanol (Found: C, 56·6; H, 4·0; N, 15·0. $C_{22}H_{19}N_5O_7$ requires C, 56·8; H, 4·1; N, 15·1%). An attempt to dehydrogenate this compound with chloranil in xylene medium resulted only in recovered indole.

Naphtho(2′,1′:1,2)*pyrido*(3″,2″:5,6)*carbazole* (VII).—1,2,3,4-*Tetrahydro*-1-*oxophenanthrene* 6-*quinolylhydrazone*, prepared from the ketone (1·5 g.), 6-quinolylhydrazine hydrochloride (1·9 g.) and sodium acetate (1·2 g.) in ethanol, formed yellow needles (2·5 g.), m. p. 279°, from chlorobenzene (Found: C, 81·6; H, 5·8; N, 12·5. $C_{23}H_{19}N_3$ requires C, 81·9; H, 5·6; N, 12·5%). Its cyclisation (2 g.) could be achieved only with more drastic conditions (30 minutes' heating and 2 vol. of sulphuric acid to 5 vol. of acetic acid); 3,4-*dihydronaphtho*(2′,1′:1,2)*pyrido*(3″,2″:5,6)-*carbazole*, insoluble in the usual organic sovents, was purified by sublimation *in vacuo* at 300°, and formed pale yellow needles (1·2 g.), m. p. 407° (Found: C, 86·6; H, 4·8; N, 8·7. $C_{23}H_{16}N_2$ requires C, 86·3; H, 5·0; N, 8·7%). This compound gave a bright red picrate, decomp. >260°, and a red addition compound with tetrachlorophthalic anhydride. Dehydrogenation, effected

[11] Buu-Hoï, Saint-Ruf, Jacquignon, and Barrett, *J.*, 1958, 4308.

by two sublimations with 2 parts of palladium–charcoal, furnished the *carbazole* (VII), lemon-yellow needles, m. p. 422° (Found: C, 87·1; H, 4·6. $C_{23}H_{14}N_2$ requires C, 86·8; H, 4·4%); the picrate crystallised as orange needles, m. p. 353° (decomp. >300°), from nitrobenzene.

Naphtho(1′,2′:1,2)*pyrido*(3″,2″:5,6)*carbazole* (VIII).—1,2,3,4-Tetrahydro-4-oxophenanthrene 6-quinolylhydrazone was obtained as a resin which was indolised by heating it for 1 hr. with sulphuric acid (4 vol.) in acetic acid (10 vol.). The crude dihydrocarbazole was dehydrogenated over palladium–charcoal, to afford the *carbazole* (VIII), pale yellow, sublimable needles, m. p. 373° (Found: C, 86·8; H, 4·1%), giving an orange-red picrate.

Naphtho(2′,1′:1,2)*pyrido*(2′,3′:7,8)*carbazole* (IX).—1,2,3,4-*Tetrahydro*-1-*oxophenanthrene* 5-*quinolylhydrazone* formed yellow needles, m. p. 232°, from benzene (Found: N, 12·8%); indolisation as for (VIII) yielded the *dihydrocarbazole*, straw-coloured needles, m. p. 348° (from benzene) (Found: C, 86·2; H, 5·0; N, 8·4%). Two sublimations over palladium–charcoal furnished the *carbazole* (IX), pale yellow needles, m. p. 391° (Found: C, 86·7; H, 4·6; N, 8·7%).

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