Carcinogenic Nitrogen Compounds. Part XVI. Some Condensed Carbazoles and their Thiophen Analogues.*

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Some condensed derivatives of carbazole, their analogues in the thiophen series, and polycyclic indoles have been synthesised for testing as potential carcinogens and as tumour-growth inhibitors.

SEVERAL condensed carbazoles, especially 1 : 2-benzocarbazoles (Lacassagne, Buu-Hoï Royer, and Zajdela, *Compt. rend. Soc. biol.*, 1947, **141**, 635) and bis-angular dibenzocarbazoles (Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429; Badger, Cook, Hewett, Kennaway, Kennaway, Martin, and Robinson, *ibid.*, 1942, **131**, 170; Kirby and Peacock, *Brit. J. Exp. Path.*, 1946, **27**, 179), have shown significant carcinogenic properties and inhibitory effects on the growth of grafted tumours (Badger, Elson, Haddow, Hewett, and Robinson, *Proc. Roy. Soc.*, 1942, *B*, **130**, 255), and it was therefore considered of interest to synthesise some even more condensed carbazole derivatives for biological testing. The present paper reports the preparation of hexacyclic compounds.

The α-naphthylhydrazone of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-oxoanthracene was converted by hydrogen chloride in acetic acid (cf. Buu-Hoï, Khôi, and Xuong, *J. Org. Chem.*, 1951, **16**, 315) into 3 : 4 : 5′ : 6′ : 7′ : 8′-hexahydro-7 : 8-benzonaphtho(2′ : 3′-1 : 2)-carbazole (I), which was partially dehydrogenated by use of 1·3 mols. of chloranil (cf. Barclay and Campbell, *J.*, 1945, 530; Buu-Hoï, Hoán, and Khôi, *J. Org. Chem.*, 1949, **14**, 492) to the tetrahydro-compound (II); dehydrogenation by 5·5 mols. of chloranil afforded the fully aromatic (III). The same sequence of reactions was followed for the

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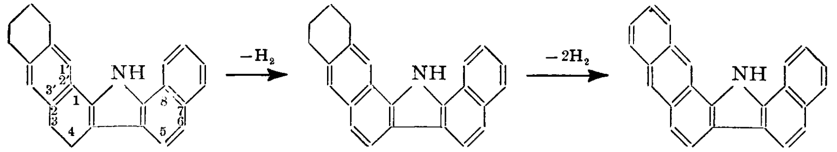
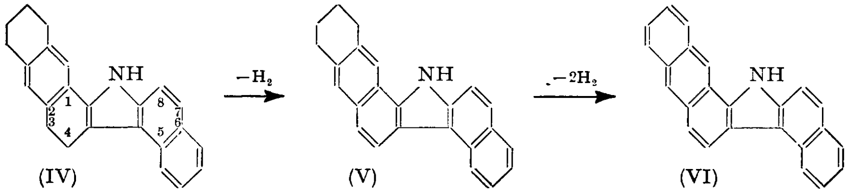
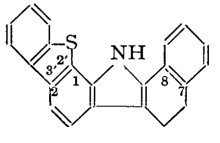
preparation of 5 : 6-benzonaphtho(2′ : 3′-1 : 2)carbazole (VI). Indole formation from the α- and the β-naphthylhydrazone of 1 : 2 : 3 : 4-tetrahydro-1-oxodibenzothiophen (Buu-Hoï, and Cagniant, *Ber.*, 1943, **76**, 1269) gave directly 7 : 8-benzo- (VII) and 5 : 6-benzothionaphtheno(2′ : 3′-1 : 2)carbazole (VIII), the intermediary dihydro-compounds being oxidised during the process.



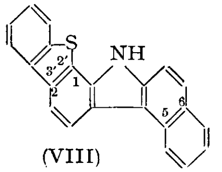
(I) (II) (III)



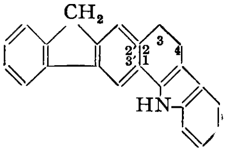
(IV) (V) (VI)



(VII)



(VIII)



(IX)

Fischer cyclisation of 2- and 3-acetylphenanthrene phenylhydrazone readily gave 2-2′- and 2-3′-phenanthrylindole respectively; from 3-*n*-butyrylpyrene phenylhydrazone, 3-ethyl-2-3′-pyrenylindole was similarly prepared. The phenylhydrazone of 1′ : 2′ : 3′ : 4′-tetrahydro-4′-oxo-2 : 3-benzofluorene readily afforded 3 : 4-dihydro-compound (IX), but dehydrogenation of this compound in the usual way failed to give a pure product.

None of the substances described here showed carcinogenic activity in mice with the skin-painting technique.

EXPERIMENTAL

3 : 4 : 5′ : 6′ : 7′ : 8′-*Hexahydro*-7 : 8-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (I).—1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-Octahydro-1-oxoanthracene, b. p. 206—207°/18 mm., m. p. 48°, was prepared from tetralin and succinic anhydride according to Krollpfeiffer and Schäfer (*Ber.*, 1923, **56**, 620), except that the β-(1 : 2 : 3 : 4-tetrahydro-1-naphthoyl)propionic acid was reduced with hydrazine hydrate and potassium hydroxide in diethylene glycol (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2478). A solution of this ketone (2 g.), α-naphthylhydrazine hydrochloride (2·6 g.), and sodium acetate (1·5 g.) in ethanol was refluxed for 1 hr., and the crude hydrazone obtained on dilution with water was treated with a boiling acetic acid solution of hydrogen chloride (20 c.c.). The precipitated *carbazole* derivative obtained on dilution with water gave on recrystallisation yellowish needles (2 g.), m. p. 187°, from benzene (Found : C, 88·8; H, 6·5. $C_{24}H_{21}N$ requires C, 89·2; H, 6·5%), giving yellow sulphuric acid solutions and a violet picrate.

5′ : 6′ : 7′ : 8′-*Tetrahydro*-7 : 8-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (II).—A solution of the foregoing substance (1 g.) and chloranil (1 g.) in dry xylene (30 c.c.) was refluxed for 2 hr.; the tetrachloroquinol was filtered off after cooling, and the filtrate washed with dilute aqueous sodium hydroxide and with water. The solid *tetrahydro*-compound obtained after removal of solvent formed pale yellow needles (0·7 g.), m. p. 217°, from benzene (Found : C, 89·4; H, 5·8. $C_{24}H_{19}N$ requires C, 89·7; H, 5·9%), giving a cherry-red sulphuric acid solution and a brown-violet picrate.

7 : 8-*Benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (III).—A solution of compound (I) (0·8 g.) and chloranil (3 g.) in dry xylene (50 c.c.) was treated as above; the dehydrogenation *product* (0·5 g.)

formed shiny greenish-yellow leaflets, m. p. 282°, from benzene, giving a violet colour with sulphuric acid (Found : C, 90·4; H, 4·8; N, 4·3. $C_{24}H_{15}N$ requires C, 90·8; H, 4·7; N, 4·4%).

3 : 4 : 5′ : 6′ : 7′ : 8-*Hexahydro*-5 : 6-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (IV).—Prepared as for the isomer (I), this *compound* formed from benzene yellowish prisms, m. p. 211° (Found : C, 88·9; H, 6·5%), giving orange sulphuric acid solutions and a violet picrate.

It gave 5′ : 6′ : 7′ : 8′-*tetrahydro*-5 : 6-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (V), pale yellow needles (from benzene), m. p. 260°, giving brown-red sulphuric acid solutions (Found : C, 89·5; H, 5·7%), and thence 5 : 6-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (VI), greenish-yellow leaflets (from xylene), m. p. 311°, giving a brown-violet colour with sulphuric acid (Found : C, 90·5; H, 4·5%).

7 : 8-*Benzothionaphtheno*(2′ : 3′-1 : 2)*carbazole* (VII).—A solution of 1 : 2 : 3 : 4-tetrahydro-1-oxodibenzothiophen (1·5 g.), α-naphthylhydrazine hydrochloride (3 g.), and sodium acetate (3 g.) was refluxed for 1 hr. in ethanol, and the crude hydrazone obtained was cyclised in the usual way (slight decomposition with evolution of hydrogen sulphide occurred during this process). The *carbazole* (1·3 g.) crystallised as shiny, grey-tinged leaflets, m. p. 266°, from benzene, giving brown-red sulphuric acid solutions (Found : C, 80·8; H, 4·6. $C_{22}H_{15}NS$ requires C, 81·2; H, 4·6%). This substance was recovered unchanged after treatment with chloranil.

5 : 6-*Benzothionaphtheno*(2′ : 3′-1 : 2)*carbazole* (VIII), prepared therefrom, crystallised as grey-tinged prisms (1·5 g.), m. p. 306°, from benzene (Found : C, 81·9; H, 4·5%), giving brown-red sulphuric acid solutions, and a red picrate.

3 : 4-*Dihydrofluoreno*(3′ : 2′-1 : 2)*carbazole* (IX).—1′ : 2′ : 3′ : 4′-Tetrahydro-4′-oxo-2 : 3-benzofluorene, m. p. 148—149°, b. p. 279—280°/21 mm., was prepared from fluorene and succinic anhydride according to Koelsch (*J. Amer. Chem. Soc.*, 1933, **55**, 3885), except that the intermediary keto-acid was reduced by the Huang-Minlon technique. A mixture of the ketone (4 g.) and phenylhydrazine was heated at 120° with removal of water, and the crude hydrazone cyclised in the usual way; the *carbazole* formed colourless prisms (4 g.), m. p. 140°, from ethanol (Found : C, 89·7; H, 5·6. $C_{23}H_{17}N$ requires C, 89·9; H, 5·5%), giving a yellow colour with sulphuric acid, and a deep violet picrate.

2-2′-*Phenanthrylindole*.—A mixture of 2-acetylphenanthrene phenylhydrazone (6 g.; yellowish needles, m. p. 190—191°, from ethanol) and freshly fused zinc chloride was heated at 200° until the reaction had subsided; aqueous acetic acid was added, and the *indole* taken up in benzene. It crystallised as grey-tinged prisms (4 g.), m. p. 237°, from ethanol (Found : C, 90·0; H, 5·3. $C_{22}H_{15}N$ requires C, 90·1; H, 5·1%). The corresponding picrate formed brown-violet needles, m. p. 205—206°, from ethanol.

2-3′-*Phenanthrylindole*.—Similar cyclisation of 3-acetylphenanthrene phenylhydrazone (6·5 g.; yellowish needles, m. p. 188—189°, from ethanol) yielded an *indole*, crystallising as grey-tinged prisms (5 g.), m. p. 160°, from ethanol (Found : C, 89·8; H, 5·1%), giving a brown-violet picrate.

3-*Ethyl*-2-3′-*pyrenylindole*.—Cyclisation of 3-*n*-butyrylpyrene phenylhydrazone (3 g.), effected with acetic acid and hydrogen chloride, afforded an *indole*, crystallising from ethanol as yellowish needles, m. p. 147° (Found : C, 90·1; H, 5·4. $C_{26}H_{19}N$ requires C, 90·4; H, 5·5%), giving a red picrate.

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