302. *Carcinogenic Nitrogen Compounds. Part XVIII.* The Synthesis of Some Polycyclic Carbazoles.*

By Ng. Ph. Buu-Hoï and Pierre Jacquignon.

New syntheses are reported for some known polycyclic carbazoles, and several new highly condensed carbazoles and their thiophen analogues have been prepared for biological evaluation of potential carcinogenic or carcinostatic activity.

Whereas among aromatic hydrocarbons and in the acridine group significant carcinogenic activity is already encountered in tetracyclic derivatives (*e.g.*, 1 : 2-benzanthracenes and 1 : 2-benzacridines), in the carbazole series pronounced activity is reached only with pentacyclic molecules (*e.g.*, 3 : 4-5 : 6-dibenzocarbazole).[1] This suggested the preparation of further carbazoles having five or more rings, and their testing for carcinogenic, and the related tumour-growth inhibiting, activity.

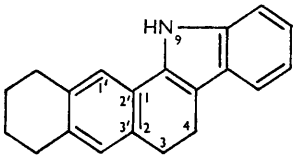
Naphtho(2′ : 3′-1 : 2)carbazole (III; R = H), first synthesised by von Braun and Bayer,[2] was now prepared by Fischer cyclisation of the phenylhydrazone of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-oxoanthracene, and dehydrogenation of the resulting 3 : 4 : 5′ : 6′ : 7′ : 8′-hexahydronaphtho(2′ : 3′-1 : 2)carbazole (I) with chloranil in excess; when only 1 mol. of chloranil was used, partial dehydrogenation occurred, and the 5′ : 6′ : 7′ : 8′-tetrahydro-derivative (II) was obtained. 6-Methylnaphtho(2′ : 3′-1 : 2)-carbazole (III; R = Me) was prepared in the same way. Thionaphtheno(2′ : 3′-1 : 2)-carbazole (IV; R = H) and its 6-methyl derivative (IV; R = Me), thiophen isologues of (III) with very similar properties, were obtained from 1 : 2 : 3 : 4-tetrahydro-1-oxodibenzothiophen. Another group of pentacyclic derivatives of carbazole was prepared from 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene; the phenylhydrazone of this ketone underwent cyclisation to 3 : 4-dihydronaphtho(2′ : 1′-1 : 2)carbazole (V; R = H), which was

* Part XVII, Buu-Hoï, Royer, and Hubert-Habart, *J.*, 1955, 1082.

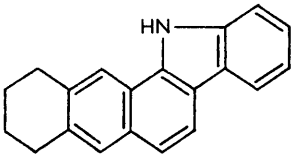
[1] Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429; Badger, Cook, Kennaway, Kennaway, Martin, and Robinson, *ibid.*, 1942, **131**, 170; Kirby and Peacock, *Brit. J. Exp. Path.*, 1946, **27**, 179; Lacassagne, Buu-Hoï, Royer, and Zajdela, *Compt. rend. Soc. biol.*, 1947, **141**, 635; Lacassagne, Buu-Hoï, Zajdela, and Xuong, *Bull. Cancer*, 1955, **42**, 3.

[2] Von Braun and Bayer, *Annalen*, 1929, **472**, 101.

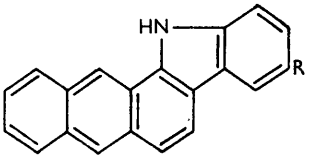
dehydrogenated by chloranil to the naphthocarbazole (VI; R = H). The phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-4-oxophenanthrene was indolised to 3 : 4-dihydronaphtho(1′ : 2′-1 : 2)carbazole (VII; R = H), whose low melting point contrasted with the high melting point of its isomer (V; R = H); the methyl compound (VII; R = Me), similarly prepared, likewise had a very low melting point. It is interesting that, in the acridine series of analogous structure, the cinchoninic acid (VIII), obtained from the same ketone by a Pfitzinger reaction, has a normal melting point.



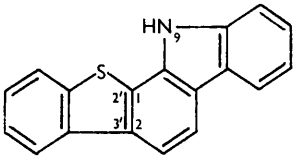
(I)



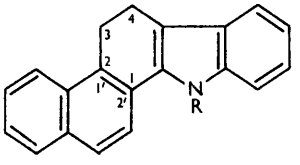
(II)



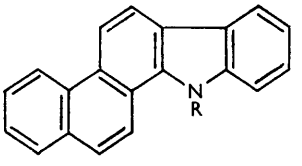
(III)



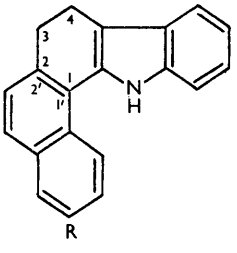
(IV)



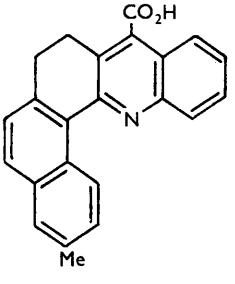
(V)



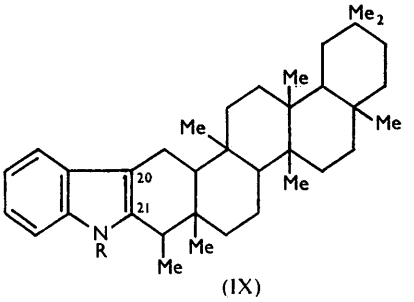
(VI)



(VII)



(VIII)



(IX)

N-Alkylphenylhydrazines proved convenient for the synthesis of polycyclic 9-alkylcarbazoles; thus, 9-methylnaphtho(2′ : 1′-1 : 2)carbazole (VI; R = Me) was readily prepared *via* the 3 : 4-dihydro-compound (V; R = Me). This method, applied to the preparation of the carcinogenic 9-methyl-1 : 2-benzocarbazole, was an improvement on the previous *N*-methylation procedure.[3]

Two heptacyclic compounds of the same series, indolo(3′ : 2′-20 : 21)friedelene (IX; R = H) and its 1′-methyl derivative (IX; R = Me), were prepared by indolisation of the phenylhydrazone and *N*-methylphenylhydrazone of friedelin, a saturated ketone extracted from cork.[4]

During this work, it was observed that compounds of the carbazole series form well-crystallised, deeply coloured addition complexes with one mol. of tetrachlorophthalic anhydride,[5] and these complexes are often more suitable for characterisation than the picrates.

The new carbazoles reported here are under biological examination in this Institute (Dr. Zajdela) for carcinogenic activity.

[3] Buu-Hoï, *J.*, 1946, 795.

[4] Drake and Jacobsen, *J. Amer. Chem. Soc.*, 1935, **57**, 1570; Ruzicka, Jeger, and Ringnes, *Helv. Chim. Acta*, 1944, **27**, 972; Dutler, Jeger, and Ruzicka, *ibid.*, 1955, **38**, 1268.

[5] Cf. Pfeiffer, *Ber.*, 1922, **55**, 413; Buu-Hoï and Jacquignon, *Compt. rend.*, 1952, **234**, 1056.

Experimental

3 : 4 : 5′ : 6′ : 7′ : 8′-*Hexahydronaphtho*(3′ : 2′-1 : 2)*carbazole* (I).—A mixture of phenylhydrazine (2 g.) and 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-oxoanthracene (2 g.; prepared from tetralin and succinic anhydride [6]) was heated at 120—130° until water ceased to be evolved, and the crude hydrazone was heated with an acetic acid solution of hydrogen chloride (20 c.c.) for a few seconds. After cooling, water was added, and the cyclisation *product* taken up in benzene; recrystallisation from *cyclo*hexane afforded leaflets (2 g.), m. p. 215°, giving a yellow halochromy in sulphuric acid and a dark violet picrate (Found: C, 87·6; H, 6·9. $C_{20}H_{19}N$ requires C, 87·9; H, 7·0%).

5′ : 6′ : 7′ : 8′-*Tetrahydronaphtho*(2′ : 3′-1 : 2)*carbazole* (II).—A solution of the foregoing hexahydro-compound (5 g.) in dry xylene (100 c.c.) was refluxed with chloranil (5 g.) for 12 hr. After cooling, the precipitated tetrachloroquinol was filtered off, and the xylene layer washed with 10% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). The residue left on evaporation of the solvent crystallised as grey-tinged needles (3 g.), m. p. 273°, from *cyclo*hexane (Found: C, 88·3; H, 6·2. $C_{20}H_{17}N$ requires C, 88·6; H, 6·3%). This *carbazole* gave a violet picrate and a deep yellow halochromy in sulphuric acid.

Naphtho(2′ : 3′-1 : 2)*carbazole* (III).—The foregoing tetrahydro-compound (5 g.) was dehydrogenated with chloranil (15 g.) in xylene (100 c.c.) as above. The dehydrogenation product formed pale yellow leaflets (3·5 g.), m. p. 327°, from *cyclo*hexane and gave an orange-yellow halochromy in sulphuric acid; von Braun and Bayer [2] gave m. p. 325°.

3 : 4 : 5′ : 6′ : 7′ : 8′-*Hexahydro*-6-*methylnaphtho*(2′ : 3′-1 : 2)*carbazole*.—A solution of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-oxoanthracene (4 g.), *p*-tolylhydrazine hydrochloride (3·6 g.), and sodium acetate (2·6 g.) in ethanol was refluxed for 1 hr., and the crude *p*-tolylhydrazone which was precipitated on dilution with water was collected and indolised in the usual way. The resulting *hexahydrocarbazole* formed prisms (3·5 g.), m. p. 242°, from *cyclo*hexane and gave a lemon-yellow halochromy in sulphuric acid and a violet picrate (Found: C, 87·6; H, 7·4. $C_{21}H_{21}N$ requires C, 87·8; H, 7·3%).

6-*Methylnaphtho*(2′ : 3′-1 : 2)*carbazole* (III; R = Me).—Dehydrogenation of the foregoing compound (1·5 g.) with chloranil (4·4 g.) afforded a *carbazole*, crystallising from *cyclo*hexane as pale yellow needles (1 g.), m. p. >340° (Found: C, 89·5; H, 5·3. $C_{21}H_{15}N$ requires C, 89·7; H, 5·3%).

Thionaphtheno(2′ : 3′-1 : 2)*carbazole* (IV; R = H).—The crude hydrazone from 1 : 2 : 3 : 4-tetrahydro-1-oxodibenzothiophen [7] (1·5 g.) and phenylhydrazine (2·4 g.) underwent partial decomposition on indolisation; the crude product yielded, on dehydrogenation with chloranil (1 g.), a *carbazole*, crystallising as colourless, sublimable leaflets (from benzene), m. p. >340°, giving an orange-yellow halochromy with sulphuric acid (Found: C, 78·8; H, 4·5. $C_{18}H_{13}NS$ requires C, 78·5; H, 4·7%).

6-*Methylthionaphtheno*(2′ : 3′-1 : 2)*carbazole* (IV; R = Me).—Similarly prepared from *p*-tolylhydrazine hydrochloride (2·5 g.), and dehydrogenation of the intermediary dihydrocarbazole (1·2 g.) with chloranil (1·2 g.), this *compound* formed colourless, sublimable leaflets (from benzene), m. p. and halochromy as for its analogue (Found: C, 79·1; H, 5·0. $C_{19}H_{15}NS$ requires C, 78·9; H, 5·2%).

3 : 4-*Dihydronaphtho*(2′ : 1′-1 : 2)*carbazole* (V; R = H).—A mixture of 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene [8] (5 g.) and phenylhydrazine (5 g.) was heated at 120—130° for a few minutes, and the crude hydrazone indolised in the usual way. The *dihydro-compound* (5 g.) formed colourless needles, m. p. 281°, from ethanol–benzene (Found: C, 88·9; H, 5·7. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6%). *Naphtho*(2′ : 1′-1 : 2)*carbazole* (VI; R = H), obtained on dehydrogenation with chloranil, formed yellowish, sublimable prisms, m. p. >340°, from ethanol (Found: C, 89·7; H, 5·0. $C_{20}H_{13}N$ requires C, 89·9; H, 4·9%); its picrate formed dark violet needles, m. p. 193—194°, from ethanol.

3 : 4-*Dihydro*-9-*methylnaphtho*(2′ : 1′-1 : 2)*carbazole* (V; R = Me).—A mixture of the oxophenanthrene (2 g.) and *N*-methylphenylhydrazine (2 g.) was heated at 120°; the crude hydrazone yielded on indolisation a *dihydro-compound* (1·4 g.), crystallising as yellowish needles, m. p. 198°, from light petroleum (Found: C, 89·2; H, 6·1. $C_{21}H_{17}N$ requires C, 89·0; H, 6·0%). This gave a picrate which crystallised as dark violet needles, m. p. 192—193° (darkening

[6] Cf. Buu-Hoï and Jacquignon, *J.*, 1954, 513.
[7] Buu-Hoï and Cagniant, *Ber.*, 1943, **76**, 1269.
[8] Haworth, *J.*, 1932, 1125.

above 180°), from ethanol, and a stable *addition complex* with tetrachlorophthalic anhydride which crystallised as red needles, m. p. 183—184°, from acetic acid (Found: C, 60·9; H, 3·3. $C_{29}H_{17}O_3NCl_4$ requires C, 61·2; H, 3·0%).

9-*Methylnaphtho*(2′ : 1′-1 : 2)*carbazole* (VI; R = Me).—A solution of the foregoing dihydro-compound (1 g.) and chloranil (1 g.) in xylene was refluxed for 3 hr. The dehydrogenation *product* formed yellowish leaflets, m. p. 268° (from *cyclo*hexane) (Found: C, 89·5; H, 5·2. $C_{21}H_{15}N$ requires C, 89·7; H, 5·3%), giving a violet picrate.

3 : 4-*Dihydro*-9-*methyl*-1 : 2-*benzocarbazole*.—Obtained from α-tetralone (2 g.) and *N*-methylphenylhydrazine (2 g.), this compound crystallised as colourless leaflets, m. p. 134°, from ethanol (Found: C, 87·8; H, 6·5. Calc. for $C_{17}H_{15}N$: C, 87·6; H, 6·4%); the picrate decomposed on recrystallisation, but the addition product with one mol. of tetrachlorophthalic anhydride formed stable red needles, m. p. 121—122°, from acetic acid. Dehydrogenation of this dihydro-compound with chloranil (12 hours' heating) afforded a 78% yield of 9-methyl-1 : 2-benzocarbazole, m. p. 169°, from *cyclo*hexane (lit.,[3] m. p. 168°).

3 : 4-*Dihydronaphtho*(1′ : 2′-1 : 2)*carbazole* (VII; R = H).—1 : 2 : 3 : 4-Tetrahydro-4-oxophenanthrene [8] (2 g.) was condensed with phenylhydrazine (2 g.); the crude hydrazone gave on indolisation a resin which was purified *via* its picrate (brown-violet needles, m. p. 176°, from methanol). Decomposition of this picrate (1·5 g.) with aqueous ammonia, and repeated crystallisation of the free *dihydrocarbazole* from light petroleum, afforded colourless needles, m. p. 118° (Found: C, 89·5; H, 5·5. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6%).

3 : 4-*Dihydro*-6′-*methylnaphtho*(1′ : 2′-1 : 2)*carbazole* (VII; R = Me), prepared from 1 : 2 : 3 : 4-tetrahydro-7-methyl-4-oxophenanthrene (2 g.) and phenylhydrazine (2 g.), was purified *via* its picrate (dark violet needles, m. p. 187°, from methanol), and formed colourless needles, m. p. 133°, from light petroleum (Found: C, 89·2; H, 5·9. $C_{21}H_{17}N$ requires C, 89·0; H, 6·0%).

3 : 4-*Dihydro*-6′-*methylnaphtho*(1′ : 2′-1 : 2)*acridine*-5-*carboxylic Acid* (VIII).—A solution of isatin (0·8 g.), 1 : 2 : 3 : 4-tetrahydro-7-methyl-4-oxophenanthrene (1 g.), and potassium hydroxide (0·8 g., dissolved in 1 c.c. of water) in ethanol (10 c.c.) was refluxed for 12 hr. The product was poured in water, the neutral impurities were removed with benzene, and the aqueous layer was acidified with acetic acid. The *cinchoninic acid* (1·1 g.) formed yellow prisms, m. p. 323—324° (decomp. from 312°), from ethanol (Found: C, 81·3; H, 5·0. $C_{23}H_{17}O_2N$ requires C, 81·4; H, 5·0%).

Indolo(3′ : 2′-20 : 21)*friedelene* (IX; R = H).—A mixture of friedelin (0·7 g.; m. p. 257—258°) and phenylhydrazine (1 g.) was heated at 130° for 30 min.; the crude *phenylhydrazone* (which could not be prepared in ethanol) yielded on cyclisation a product crystallising from ethanol–benzene as colourless prisms (0·5 g.), m. p. 309—310°, giving a brown-violet colour in ethanolic picric acid (Found: C, 86·2; H, 10·5. $C_{36}H_{53}N$ requires C, 86·6; H, 10·6%). 1′-*Methylindolo*(3′ : 2′-20 : 21)*friedelene* (IX; R = Me), prepared from friedelin (0·7 g.) and *N*-methylphenylhydrazine (1 g.), formed colourless prisms, m. p. 217—218°, from ethanol (Found: C, 86·2; H, 10·5. $C_{37}H_{55}N$ requires C, 86·5; H, 10·7%).

This work is part of a cancer research scheme (Professor A. Lacassagne) supported by a grant from the U.S. Department of Health, Education, and Welfare; the authors thank the authorities concerned. They also express gratitude to Professor G. Ourisson (Strasbourg) for the generous gift of friedelin, and to Miss Patricia F. Boshell, M.A., for assistance.

THE RADIUM INSTITUTE, UNIVERSITY OF PARIS. [*Received, October* 31*st*, 1955.]