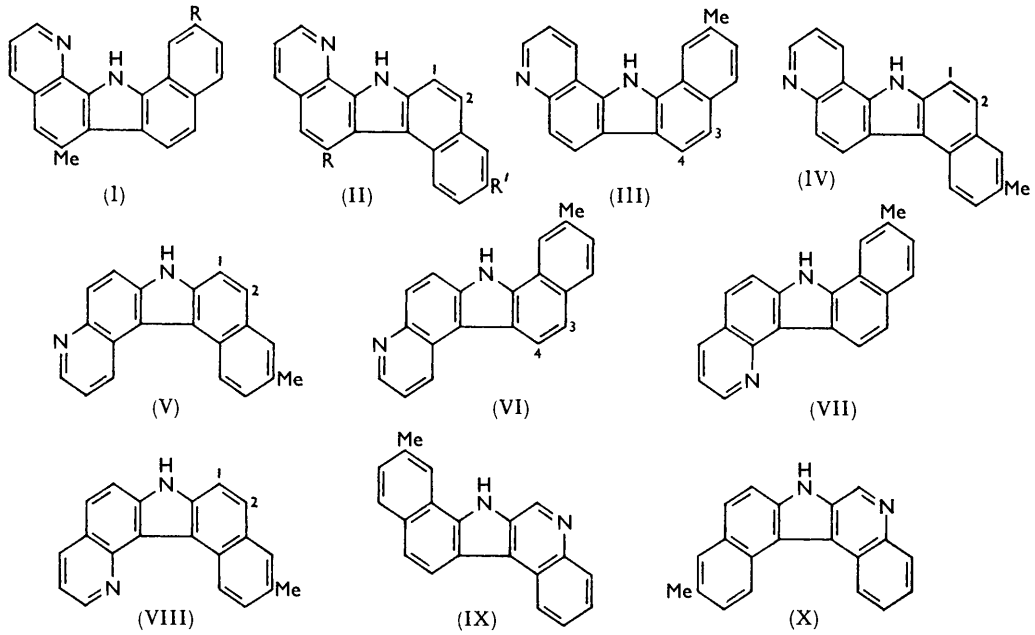
909. *Carcinogenic Nitrogen Compounds. Part XXXVII.*[1] *Some Isosteres and Homologues of the Carcinogenic Benzopyridocarbazoles.*

By N. P. Buu-Hoï, P. Jacquignon, and J. P. Hoeffinger.

Several thiophen isosteres and mono- and di-methyl homologues of the carcinogenic bisangular benzopyridocarbazoles have been synthesised from quinolylhydrazines for determination of their biological activity.

Many bisangular benzopyridocarbazoles are carcinogenic; some are extremely powerful sarcomogens by subcutaneous injection in mice [2] and also elicit epitheliomas of the stomach by ingestion.[3] Interestingly, these compounds, which can be considered as isosteres of the bisangular dibenzocarbazoles (well known for their hepatoma-inducing properties [4]), showed no activity whatsoever on the liver, even by ingestion. This points to a basic difference between this new group of carcinogens and the dibenzocarbazoles, and hence further benzopyridocarbazoles and analogous compounds were prepared, for testing and establishment of relationships between their structures and activities. The synthesis is reported here of a number of mono- and di-methyl homologues of eight types of bisangular

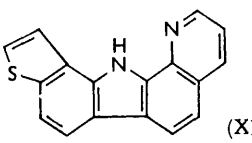


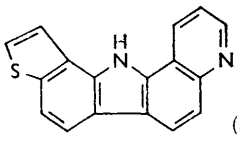
benzopyridocarbazole, (I)—(VIII), and of two types of bisangular dibenzocarboline (IX) and (X). The monomethyl derivatives were obtained from methylquinolylhydrazones of 1- and 2-tetralone, and quinolylhydrazones of methyltetralones, and the dimethyl homologues were obtained from methylquinolylhydrazones of methyltetralones. Here, as previously noted,[5] indolisation with sulphuric acid in acetic acid gave the corresponding dihydrocarbazoles whilst anhydrous zinc chloride brought about simultaneous dehydrogenation to yield the carbazole directly. Whereas there is no question as to the structure

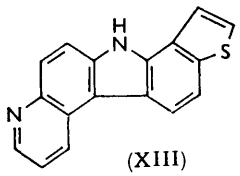
[1] Part XXXVI, Buu-Hoï, Saint-Ruf, Jacquignon, and Marty, *J.*, 1963, 2274.
[2] Lacassagne, Buu-Hoï, Zajdela, Périn, and Jacquignon, *Nature*, 1961, **191**, 1005.
[3] Lacassagne, Buu-Hoï, Zajdela, Jacquignon, and Périn, *Compt. rend.*, 1963, **257**, 818.
[4] Boyland and Brues, *Proc. Roy. Soc.*, 1957, *B*, **122**, 429; Boyland and Mawson, *Biochem. J.*, 1938, **32**, 1460.
[5] Buu-Hoï, Périn, and Jacquignon, *J.*, 1960, 4500.

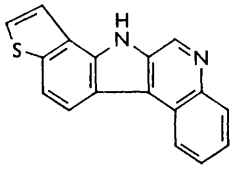
of the carbazoles derived from 5- and 8-quinolylhydrazine, cyclisation of 3-, 6-, and 7-quinolylhydrazones could in theory lead to either linear or angular structures; that the compounds obtained were angular was shown by their ultraviolet spectra, which were similar to those of the corresponding bisangular dibenzocarbazoles (Figs. 1 and 2).

Carcinogenic polycyclic hydrocarbons often retain biological activity when a benzene ring in the molecule is replaced by a thiophen one,[6] and so we prepared several thiophen isosteres of benzopyridocarbazoles, by zinc chloride indolisation of the appropriate


(XI)


(XII)


(XIII)


(XIV)

quinolylhydrazones of 4,5,6,7-tetrahydro-4-oxo-1-benzothiophen; the four pyridothienocarbazoles prepared correspond to the structures (XI)—(XIV). In their properties, including their ultraviolet spectra (Fig. 2), they closely resembled their benzene analogues.

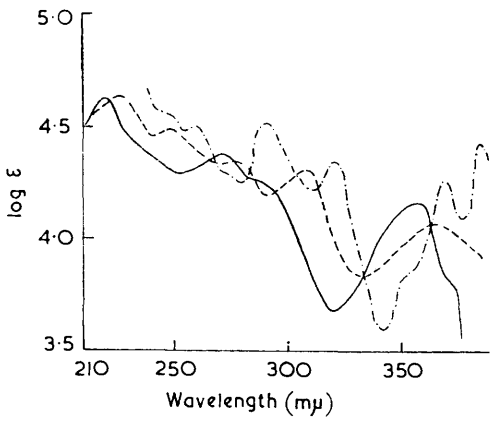


FIG. 1. Absorption spectra of (——) compound (X), (– – –) compound (V), and (— · — ·) 3,4:5,6-dibenzocarbazole.

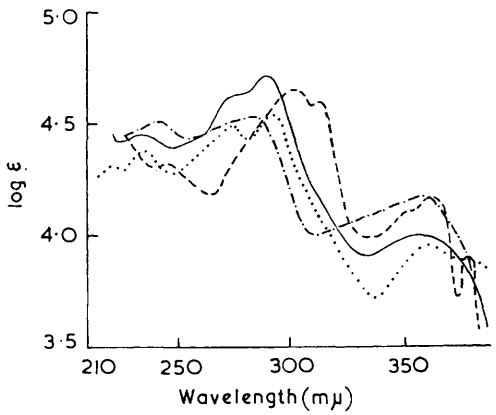


FIG. 2. Absorption spectra of (——) compound (VII), (· · ·) compound (VI), (— · — ·) compound (XIII), and (– – –) 1,2:4,5-dibenzocarbazole.

Evaluation, by subcutaneous injection in mice, of the sarcomogenic activity of the methylated benzopyridocarbazoles described herein showed that substitution is strongly prejudicial to this type of biological activity, all the substances tested being either completely inactive or only very slightly carcinogenic; this was also the case with the previously described hexacyclic naphthopyridocarbazoles,[5,7] all of which were totally inactive. To a greater degree than in the other similar series of carcinogens (benzacridines,[8]

[6] A list of thiophen carcinogens is given by Buu-Hoï in " Medizinische Grundlagenforschung," Vol. II, Thieme Verlag, Stuttgart, 1959, p. 465.

[7] Buu-Hoï, Périn, and Jacquignon, *J.*, 1962, 146.

[8] Cf. Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.

benzocarbazoles,[9] and tricycloquinazolines [10]), biological activity in this group seems thus to depend on more stringent steric requirements.

Experimental *

Intermediates.—3-, 5-, 6-, 7-, and 8-quinolylhydrazine were prepared by routine methods.[11] 6-Methyl-8-nitroquinoline (39 g.), b. p. 244°/30 mm., m. p. 122° (from ethanol) (lit.,[12] m. p. 122°), was obtained from 4-amino-3-nitrotoluene (50 g.) by a Skraup reaction with glycerol (110 g.), sulphuric acid (60 c.c.), and arsenic acid (52 g.); reduction with iron and acetic acid according to Linsker and Evans's technique [13] afforded 8-amino-6-methylquinoline (22 g.), b. p. 178°/21 mm., m. p. 64°; this was converted in the usual way into 6-*methyl*-8-*quinolylhydrazine*, which formed straw-coloured needles, m. p. 107° (from cyclohexane) (Found: N, 24·0. $C_{10}H_{11}N_3$ requires N, 24·3%). 1-Tetralone, 7-methyl-1-tetralone, and 4,5,6,7-tetrahydro-4-oxo-1-benzothiophen were prepared by cyclisation of the appropriate γ-butyryl chlorides; 2-tetralone and 6-methyl-2-tetralone were prepared by reduction of the corresponding methoxynaphthalenes.[14]

Quinolylhydrazones.—These (Table 1) were prepared by refluxing a solution of the tetralone (1 mol.) and the quinolylhydrazine dihydrochloride (1 mol.) in aqueous ethanol with sodium

Table 1.

Compound	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
Derivatives of 1-tetralone								
7-Me 3-quinolylhydrazone	144°	$C_{20}H_{19}N_3$	79·4	6·2	14·1	79·7	6·3	13·9
7-Me 6-quinolylhydrazone	234		79·7	6·1	14·0			
7-Me 7-quinolylhydrazone	237		79·4	6·4	14·0			
7-Me 8-quinolylhydrazone	178		79·8	6·3	13·8			
6-Methyl-8-quinolylhydrazone	168		79·7	6·6	13·7			
7-Me 6-methyl-8-quinolylhydrazone	211	$C_{21}H_{21}N_3$	—	—	13·2	—	—	13·3
Derivatives of 4,5,6,7-tetrahydro-4-oxo-1-benzothiophen								
3-Quinolylhydrazone	189°	$C_{17}H_{15}N_3S$	—	—	14·0	69·6	5·2	14·3
5-Quinolylhydrazone	247		69·8	5·1	14·2			
6-Quinolylhydrazone	213		—	—	14·1			
8-Quinolylhydrazone	197		—	—	14·1			

acetate for 1 hr., and subsequent basification with aqueous ammonia; most of the quinolylhydrazones could be recrystallised from ethanol or benzene as golden yellow to beige needles, but some formed viscous resins which did not solidify. In the case of the 5-, 6-, and 8-quinolylhydrazones of 6-methyl-2-tetralone, spontaneous cyclisation occurred during the preparation of the hydrazone, under the influence of the acetic acid present.

Benzopyridocarbazoles.—These were prepared as described in a previous paper,[7] with a mixture of sulphuric and acetic acid, to give the corresponding dihydrocarbazole, or by heating with freshly-fused zinc chloride at 280—300° for 45 min., to give the carbazole directly; dihydrocarbazoles were dehydrogenated by repeated sublimation over 5% palladium–charcoal (chloranil in boiling xylene could also be used but the yields and quality of the products were inferior). The carbazoles were recrystallised from ethanol or benzene, or from ethanol–benzene, to give cream to pale yellow silky needles, which could be further purified by sublimation *in vacuo*. The compounds are listed in Table 2 along with their picrates, which formed bright yellow to red needles from ethanol (for the soluble substances) or chlorobenzene or nitrobenzene (insoluble ones).

* The nomenclature for carbolines adopted in this Paper is that recommended by the I.U.P.A.C., and differs from the one used in the previous Paper (*J.*, 1962, 146).

[9] Cf. Lacassagne, Buu-Hoï, Zajdela, and Xuong, *Bull. Cancer*, 1955, **42**, 3.

[10] Baldwin, Cunningham, and Partridge, communication to Internat. Cancer Congress, Moscow 1962.

[11] Wieland and Horner, *Annalen*, 1938, **536**, 92; Clemo and Swan, *J.*, 1945, 867.

[12] Bartow and McCollum, *J. Amer. Chem. Soc.*, 1904, **26**, 702.

[13] Linsker and Evans, *J. Amer. Chem. Soc.*, 1946, **68**, 149.

[14] Cornforth, Cornforth, and Robinson, *J.*, 1942, 689; Royer and Buu-Hoï, *Compt. rend.*, 1946, **222**, 746.

TABLE 2.

Benzopyrido- and pyridothieno-carbazoles.

Carbazole	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(I; R = H)	279°	$C_{20}H_{14}N_2$	85·1	5·1	9·9	85·1	5·0	9·9
picrate	285 (decomp. >265)	$C_{26}H_{17}N_5O_7$	—	—	13·5	—	—	13·7
(I; R = Me)	228	$C_{21}H_{16}N_2$	85·0	5·1	9·8	85·1	5·4	9·8
picrate	280 (decomp. >260)	$C_{27}H_{19}N_5O_7$	—	—	13·0	—	—	13·3
1,2-Dihydro-(II; R = Me, R′ = H)	224	$C_{20}H_{16}N_2$	—	—	9·6	—	—	9·8
picrate	278 (decomp. >270)	$C_{26}H_{19}N_5O_7$	—	—	13·2	—	—	13·6
(II; R = Me, R′ = H)	259	$C_{20}H_{14}N_2$	84·8	5·0	10·0	85·1	5·0	9·9
picrate	297 (decomp. >280)	$C_{26}H_{17}N_5O_7$	—	—	13·4	—	—	13·7
1,2-Dihydro-(II; R = R′ = Me)	214	$C_{21}H_{18}N_2$	—	—	9·7	—	—	9·4
picrate	290 (decomp. >275)	$C_{27}H_{21}N_5O_7$	—	—	13·0	—	—	13·3
(II; R = R′ = Me)	247	$C_{21}H_{16}N_2$	84·8	5·4	9·7	85·1	5·4	9·8
picrate	293 (decomp. >275)	$C_{27}H_{19}N_5O_7$	—	—	12·9	—	—	13·3
1,2-Dihydro-(II; R = H, R′ = Me)	202	$C_{20}H_{16}N_2$	84·1	5·5	10·1	84·5	5·6	9·8
picrate	312 (decomp. >270)	$C_{26}H_{19}N_5O_7$	—	—	13·6	—	—	13·6
(II; R = H, R′ = Me)	258	$C_{20}H_{14}N_2$	84·6	5·2	10·0	85·1	5·0	9·9
picrate	335	$C_{26}H_{17}N_5O_7$	—	—	13·4	—	—	13·7
3,4-Dihydro-(III)	282	$C_{20}H_{16}N_2$	84·4	5·9	9·7	84·5	5·6	9·8
picrate	305 (decomp. >265)	$C_{26}H_{19}N_5O_7$	—	—	13·4	—	—	13·6
(III)	345	$C_{20}H_{14}N_2$	84·8	5·1	9·8	85·1	5·0	9·9
picrate	314	$C_{26}H_{17}N_5O_7$	—	—	13·7	—	—	13·7
1,2-Dihydro-(IV)	342	$C_{20}H_{16}N_2$	84·1	5·8	9·9	84·5	5·6	9·8
picrate	268 (decomp. >255)	$C_{26}H_{19}N_5O_7$	—	—	13·5	—	—	13·6
(IV)	367	$C_{20}H_{14}N_2$	85·0	4·8	9·4	85·1	5·0	9·9
picrate	277 (decomp. >245)	$C_{26}H_{17}N_5O_7$	—	—	13·4	—	—	13·7
1,2-Dihydro-(V)	248	$C_{20}H_{16}N_2$	84·4	5·4	9·9	84·5	5·6	9·8
picrate	287 (decomp. >270)	$C_{26}H_{19}N_5O_7$	—	—	13·3	—	—	13·6
(V)	284	$C_{20}H_{14}N_2$	85·0	5·1	9·9	85·1	5·0	9·9
picrate	310 (decomp. >280)	$C_{26}H_{17}N_5O_7$	—	—	13·5	—	—	13·7
3,4-Dihydro-(VI)	338	$C_{20}H_{16}N_2$	84·2	5·8	10·0	84·5	5·6	9·8
picrate	318 (decomp. >287)	$C_{26}H_{19}N_5O_7$	—	—	13·5	—	—	13·6
(VI)	389	$C_{20}H_{14}N_2$	84·9	5·1	9·9	85·1	5·0	9·9
picrate	333 (decomp. >300)	$C_{26}H_{17}N_5O_7$	—	—	13·7	—	—	13·7
(VII)	239	$C_{20}H_{14}N_2$	84·8	5·2	9·8	85·1	5·0	9·9
picrate	312 (decomp. >270)	$C_{26}H_{17}N_5O_7$	—	—	13·8	—	—	13·7
1,2-Dihydro-(VIII)	205	$C_{20}H_{16}N_2$	—	—	9·9	—	—	9·8
picrate	237 (decomp. >210)	$C_{26}H_{19}N_5O_7$	—	—	13·5	—	—	13·6
(VIII)	217	$C_{20}H_{14}N_2$	—	—	9·9	—	—	9·9
picrate	250 (decomp. >225)	$C_{26}H_{17}N_5O_7$	—	—	13·9	—	—	13·7
(XI) [a]	207	$C_{17}H_{10}N_2S$	—	—	10·0 [b]	—	—	10·2
picrate	295 (decomp. >270)	$C_{23}H_{13}N_5O_7S$	—	—	13·3	—	—	13·9
(XII) [c]	305	$C_{17}H_{10}N_2S$	—	—	10·4	—	—	10·2
picrate	227 (decomp. >170)	$C_{23}H_{13}N_5O_7S$	—	—	13·3	—	—	13·9
(XIII) [c]	287	$C_{17}H_{10}N_2O$	—	—	9·9	—	—	10·2
picrate	337 (decomp. >300)	$C_{23}H_{13}N_5O_7S$	—	—	13·5	—	—	13·9

[a] All the thiophen derivatives were prepared by the zinc chloride-cyclisation method. [b] Found: S, 11·5. Calc.: S, 11·7%. [c] These substances gave poor sulphur analyses.

3''-*Methyl*-3,4:7,8-*dibenzo*-β-*carboline* (IX).—Prepared in 50% yield from the corresponding 3-quinolylhydrazone by the zinc chloride method and purified *via* the picrate, this *carboline* formed yellowish needles, m. p. 269° (from methanol) (Found: H, 5·1; N, 9·6. $C_{20}H_{14}N_2$ requires H, 5·0; N, 9·9%); *picrate*, golden-yellow prisms, had m. p. 300° (from chlorobenzene) (Found: N, 14·0. $C_{26}H_{17}N_5O_7$ requires N, 13·7%). This carboline gave very poor, non-reproducible carbon analyses.

7,8-*Dihydro*-3''-*methyl*-3,4:5,6-*dibenzo*-β-*carboline*.—Prepared by the sulphuric–acetic acid method, this *carboline* formed cream-coloured leaflets, m. p. 325° (decomp. >306°) (from ethanol) (Found: C, 84·2; H, 5·9; N, 9·8. $C_{20}H_{16}N_2$ requires C, 84·5; H, 5·6; N, 9·8%); *picrate*, orange prisms, m. p. 307° (decomp. >280°) (from ethanol) (Found: N, 13·7. $C_{26}H_{19}N_5O_7$ requires N, 13·6%).

3''-*Methyl*-3,4:5,6-*dibenzo*-β-*carboline* (X).—This crystallised as cream-coloured needles, m. p. 289°, from benzene–cyclohexane (Found: N, 9·9. $C_{20}H_{14}N_2$ requires N, 9·9%); the *picrate*, deep yellow prisms, had m. p. 260° (decomp. >240°) (from ethanol) (Found: N, 13·3. $C_{26}H_{17}N_5O_7$ requires N, 13·7%).

3,4-*Benzothieno*(2',3':7,8)-β-*carboline* (XIV). This crystallised as pale yellow needles, m. p. 305°, from benzene (Found: N, 10·0. $C_{17}H_{10}N_2S$ requires N, 10·2%); the *picrate* formed yellow needles, m. p. 269° (from ethanol) (Found: N, 13·6. $C_{23}H_{13}N_5O_7S$ requires N, 13·9%).

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