746. *Carcinogenic Nitrogen Compounds. Part XLI.*[1] *Pyridocarbazoles and Analogous Heterocycles Derived from Isoquinolylhydrazines.*

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5-Isoquinolylhydrazine and its 3-methyl homologue have been used for the synthesis of a number of potentially carcinogenic pyridocarbazoles, benzopyridocarbazoles, and related heterocycles.

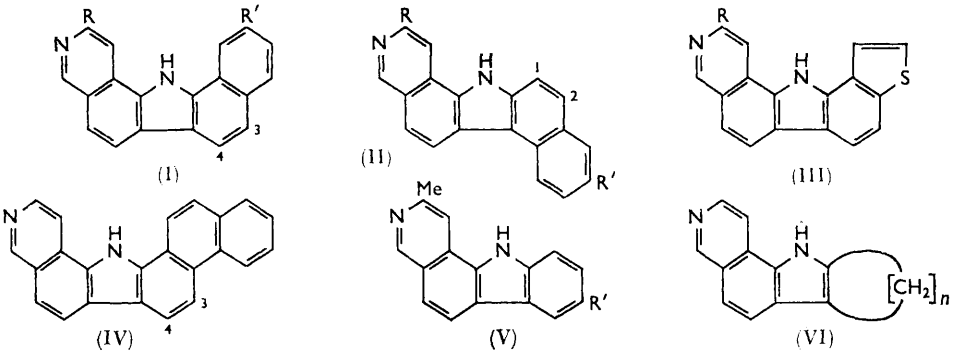
The benzopyridocarbazole group has recently been shown to contain many carcinogenic compounds, some of them extremely potent in inducing sarcomas by subcutaneous injection, and epitheliomas of the fore-stomach by ingestion.[2] This biological activity varies strikingly with the position of the pyridinic nitrogen atom, this in turn depending on the nature of the quinolylhydrazines used as intermediates for the benzopyridocarbazole syntheses.[3] It was therefore of interest to make similar use of isoquinolylhydrazines for the preparation of further benzopyridocarbazoles and related heterocycles.

5-Isoquinolylhydrazine had already been reported by Manske and Kulka,[4] who used it for the preparation of pyrido(4′,3′:1,2)carbazole;[5] and now, 3-methyl-5-isoquinolylhydrazine was synthesised from 5-amino-3-methylisoquinoline, which was readily obtained by reduction of the nitro-compound with hydrazine hydrate and Raney nickel. The hydrazones derived from 1- and 2-tetralone, and from analogous ketones, readily underwent indolisation by means of a solution of sulphuric acid in acetic acid, and gave the expected dihydrocarbazoles; but with 4,5,6,7-tetrahydro-4-oxobenzo[*b*]thiophen this method failed, and the cyclisation of its isoquinolylhydrazones had to be effected by means of zinc chloride at high temperature, this giving directly the corresponding carbazoles.

The benzopyridocarbazoles prepared belong to types (I) and (II), and the pyridothienocarbazoles to type (III); their ultraviolet spectra resemble those of their benzene analogues 1,2:5,6- and 3,4:5,6-dibenzocarbazole.[6] The naphthopyridocarbazole group is represented by compound (IV). In view of the known carcinogenic activity of 1,2-benzocarbazoles,[7] some derivatives of the isosteric heterocycle pyrido(4′,3′:1,2)carbazole (V) were prepared,

[1] Part XL, Buu-Hoï, Mabille, and Brasch, preceding Paper.
[2] Lacassagne, Buu-Hoï, Zajdela, Jacquignon, and Périn, *Compt. rend.*, 1963, **257**, 817; *Nature*, 1961, **191**, 1005.
[3] Buu-Hoï, Périn, and Jacquignon, *J.*, 1960, 4500; 1962, 146.
[4] Manske and Kulka, *Canad. J. Res.*, 1947, **25**, *B*, 376.
[5] Manske and Kulka, *Canad. J. Res.*, 1949, **27**, *B*, 291.
[6] Buu-Hoï, Jacquignon, and Hoeffinger, *J.*, 1963, 4754.
[7] Lacassagne, Buu-Hoï, Royer, and Zajdela, *Compt. rend. Soc. Biol.*, 1947, **141**, 635.

from 3-methyl-5-isoquinolylhydrazine and the appropriate cyclohexanones; indolisation of cyclopentanone and cycloheptanone 3-methyl-5-isoquinolylhydrazones afforded the pyridoindoles (VI).



The various new pyridocarbazoles are listed in the Table; results of tests for biological activity will be reported elsewhere.

Experimental

Intermediates.—Isoquinoline was nitrated according to Le Fèvre and Le Fèvre,[8] and 5-nitroisoquinoline, m. p. 110°, obtained in 86% yield, was reduced to 5-aminoisoquinoline, b. p. 210—215°/30 mm., m. p. 128°, by means of iron in acetic acid [9] (70% yield). 5-Isoquinolylhydrazine, m. p. 165°, was prepared from the amine according to Wieland and Horner's technique [10] for the preparation of quinolylhydrazines. 1-Tetralone, 7-methyl-1-tetralone, 1,2,3,4-tetrahydro-1-oxophenanthrene, and 4,5,6,7-tetrahydro-4-oxobenzo[*b*] thiophen were obtained by aluminium chloride-catalysed cyclisation of the appropriate γ-butyryl chlorides; 2-tetralone was prepared by reduction of 2-methoxynaphthalene.[11]

3-Methyl-5-isoquinolylhydrazine.—3-Methylisoquinoline was nitrated as for isoquinoline, and 3-methyl-5-nitroisoquinoline,[12] b. p. 193—195°/17 mm., m. p. 110°, was obtained in 89% yield. Its *picrate* crystallised from ethanol as lemon-yellow prisms, melting instantaneously at 188° (decomp. >160°) (Found: N, 16·7. $C_{16}H_{11}N_5O_9$ requires N, 16·8%). Reduction of the nitro-compound with 98% hydrazine hydrate and Raney nickel was effected in ethanol in the usual way, giving 5-amino-3-methylisoquinoline (70%), m. p. 218—219°; the *picrate* formed shiny yellow leaflets, m. p. 254—255° (from nitrobenzene) (Found: N, 17·8. $C_{16}H_{13}N_5O_7$ requires N, 18·1%). *3-Methyl-5-isoquinolylhydrazine*, prepared as for the lower homologue, and liberated from its tin salt complex (sandy microcrystals, m. p. 207°) by aqueous sodium hydroxide, formed golden prisms, m. p. 155° (from cyclohexane) (Found: N, 23·8. $C_{10}H_{11}N_3$ requires N, 24·3%).

2,5-Dimethyl-1-(3-methyl-5-isoquinolyl)pyrrole.—A mixture of 5-amino-3-methylisoquinoline (0·5 g.) and hexane-2,5-dione (0·5 g.) was refluxed for 30 min. with acetic acid (1 drop), and the *product* purified by distillation *in vacuo* and crystallisation from aqueous ethanol, giving shiny leaflets (0·5 g.), m. p. 99° (Found: C, 81·0; H, 7·0; N, 12·0. $C_{16}H_{16}N_2$ requires C, 81·3; H, 6·8; N, 11·9%).

Preparation of Isoquinolylhydrazones.—These were prepared by refluxing for 1—2 hr. a solution of the ketone (1 mole), the isoquinolylhydrazine dihydrochloride (1 mole), and sodium acetate (2 moles) in aqueous ethanol. Most of the hydrazones obtained on basification with aqueous ammonia were not crystallised and were directly used for cyclisation without purification; some, however, could be isolated in the crystalline state. *1-Tetralone 5-isoquinolylhydrazone* formed straw coloured needles, m. p. 188° (from ethanol) (Found: N, 14·7.

[8] Le Fèvre and Le Fèvre, *J.*, 1935, 1470.
[9] Linsker and Evans, *J. Amer. Chem. Soc.*, 1946, **68**, 149.
[10] Wieland and Horner, *Annalen*, 1938, **536**, 92.
[11] Cornforth, Cornforth, and Robinson, *J.*, 1942, 689; Royer and Buu-Hoï, *Compt. rend.*, 1946, **222**, 746.
[12] Bergström and Paterson, *J. Org. Chem.*, 1945, **10**, 479.

Pyrido-, benzopyrido-, naphthopyrido-, and pyridothieno-carbazoles.

Carbazole *	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
3,4-Dihydro-(I; R = R′ = H)	318°	—	—	10·3	$C_{19}H_{14}N_2$	—	—	10·4
picrate	323 (decomp. >300)	—	—	13·8	$C_{25}H_{17}N_5O_7$	—	—	14·0
(I; R = R′ = H)	328	84·6	4·6	10·5	$C_{19}H_{12}N_2$	85·1	4·5	10·4
3,4-Dihydro-(I; R = H, R′ = Me)	343	—	—	10·0	$C_{20}H_{16}N_2$	—	—	9·9
(I; R = H, R′ = Me)	359	—	—	9·6	$C_{20}H_{14}N_2$	—	—	9·9
3,4-Dihydro-(I; R = Me, R′ = H)	331	84·0	5·6	—	$C_{20}H_{16}N_2$	84·5	5·3	—
picrate	306 (decomp. >265)	—	—	13·2	$C_{26}H_{19}N_5O_7$	—	—	13·6
(I; R = Me, R′ = H)	337	85·2	5·1	10·0	$C_{20}H_{14}N_2$	85·1	5·0	9·9
picrate	317	—	—	13·6	$C_{26}H_{17}N_5O_7$	—	—	13·7
3,4-Dihydro-(I; R = R′ = Me)	348	84·0	5·9	9·6	$C_{21}H_{18}N_2$	84·5	6·1	9·4
picrate	306	—	—	13·2	$C_{27}H_{21}N_5O_7$	—	—	13·3
(I; R = R′ = Me)	360	84·5	5·5	9·6	$C_{21}H_{16}N_2$	85·1	5·4	9·5
picrate	323	—	—	13·1	$C_{27}H_{19}N_5O_7$	—	—	13·3
1,2-Dihydro-(II; R = R′ = H)	305	—	—	10·4	$C_{19}H_{14}N_2$	—	—	10·4
picrate	299 (decomp. >270)	—	—	14·3	$C_{25}H_{17}N_5O_7$	—	—	14·0
(II; R = R′ = H)	317	—	—	10·3	$C_{19}H_{12}N_2$	—	—	10·4
picrate	307 (decomp. >300)	—	—	13·7	$C_{25}H_{15}N_5O_7$	—	—	14·1
1,2-Dihydro(II; R = Me, R′ = H)	310	85·1	5·6	10·1	$C_{20}H_{16}N_2$	84·5	5·6	9·9
picrate	269 (decomp. >245)	—	—	13·6	$C_{26}H_{19}N_5O_7$	—	—	13·6
(II; R = Me, R′ = H) †	344	85·6	5·3	9·6	$C_{20}H_{14}N_2$	85·1	5·0	9·9
picrate	349 (decomp. >295)	—	—	13·4	$C_{26}H_{17}N_5O_7$	—	—	13·4
1,2-Dihydro-(II; R = R′ = Me)	355	84·0	5·7	9·6	$C_{21}H_{18}N_2$	84·5	6·1	9·4
picrate	346 (decomp. >260)	—	—	13·6	$C_{27}H_{21}N_5O_7$	—	—	13·3
(II; R = R′ = Me)	361	84·6	5·6	9·7	$C_{21}H_{16}N_2$	85·1	5·4	9·5
picrate	366 (decomp. >270)	—	—	13·4	$C_{27}H_{19}N_5O_7$	—	—	13·3
Picrate of (III; R = H)	270 (decomp. >250)	—	—	13·7	$C_{23}H_{13}N_5O_7S$	—	—	13·9
(III; R = Me)	318	—	—	9·7	$C_{18}H_{12}N_2S$	—	—	9·7
picrate	297 (decomp. >270)	—	—	13·2	$C_{24}H_{15}N_5O_7S$	—	—	13·5
3,4-Dihydro-(IV)	361	—	—	8·6	$C_{23}H_{16}N_2$	—	—	8·7
picrate	334	—	—	13·0	$C_{29}H_{19}N_5O_7$	—	—	12·8
(IV)	390	—	—	9·1	$C_{23}H_{14}N_2$	—	—	8·8
5,6,7,8-Tetrahydro-(V; R = H)	228	81·0	6·8	12·1	$C_{16}H_{16}N_2$	81·3	6·8	11·9
picrate	298	—	—	15·1	$C_{22}H_{19}N_5O_7$	—	—	15·1
(V; R = H)	283	83·2	5·2	12·4	$C_{16}H_{12}N_2$	82·7	5·2	12·1
picrate	276 (decomp. >266)	—	—	15·6	$C_{22}H_{15}N_5O_7$	—	—	15·2
5,6,7,8-Tetrahydro-(V; R = Me)	255	81·6	7·3	11·5	$C_{17}H_{18}N_2$	81·6	7·2	11·2
picrate	270 (decomp. >250)	—	—	14·6	$C_{23}H_{21}N_5O_7$	—	—	14·6
(V; R = Me)	284	82·4	5·9	11·2	$C_{17}H_{14}N_2$	82·9	5·7	11·4
picrate	335 (sublim. >250)	—	—	14·5	$C_{23}H_{17}N_5O_7$	—	—	14·7

* Many substances in this group gave very poor carbon analyses. † This carbazole showed three main absorption bands at 250—260, 300—310, and 350 mμ (in ethanol).

$C_{19}H_{17}N_3$ requires N, 14·6%); 1,2,3,4-*tetrahydro*-1-*oxophenanthrene* 5-*isoquinolylhydrazone* crystallised as bright yellow prisms, m. p. 223° (from toluene) (Found: N, 12·2. $C_{23}H_{19}N_3$ requires N, 12·5%); 4,5,6,7-*tetrahydro*-4-*oxobenzo*[b]*thiophen* 5-*isoquinolylhydrazone* formed canary-yellow needles, m. p. 222° (from ethanol) (Found: N, 14·0. $C_{17}H_{15}N_3S$ requires N, 14·3%).

Cyclisation Methods.—(*a*) A mixture of the isoquinolylhydrazone (1 g.), acetic acid (5 c.c.), and sulphuric acid (1 c.c.) was heated for 10 min. at 100°, and the precipitate of the dihydrocarbazole, obtained on cooling and basification with aqueous ammonia, was purified by crystallisation from ethanol or ethanol–benzene (yields 70—85%). Dehydrogenation was

effected, in almost quantitative yields, by sublimation with 5% palladium–charcoal, and the carbazole obtained was recrystallised from ethanol. All the carbazoles were colourless, sublimable compounds, with yellow to orange-yellow picrates which were recrystallised from nitrobenzene or *o*-dichlorobenzene.

(*b*) A mixture of the hydrazone (1 g.) and anhydrous zinc chloride (2 g.) was heated for 45 min. at 290°, and the product was worked up in the usual way, giving directly the carbazole.

6′-*Methyl*-2,3-*trimethylenepyrido*(3′,4′:6,7)*indole* (VI; $n = 3$).—Prepared by cyclisation of cyclopentanone 3-methyl-5-isoquinolylhydrazone by means of acetic–sulphuric acid, this *indole* formed shiny leaflets, m. p. 237° (sublim. >200°) (from benzene) (Found: C, 81·5; H, 6·3. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·4%); the *picrate* formed orange prisms, m. p. 282° (decomp. >245°) (from *o*-dichlorobenzene) (Found: N, 15·1. $C_{21}H_{17}N_5O_7$ requires N, 15·5%).

6′-*Methyl*-2,3-*pentamethylenepyrido*(3′,4′:6,7)*indole* (VI; $n = 5$).—Similarly prepared, using cycloheptanone, this *indole* formed shiny needles, m. p. 237° (sublim. >215°) (from benzene) (Found: C, 81·0; H, 7·2; N, 11·5. $C_{17}H_{18}N_2$ requires C, 81·6; H, 7·2; N, 11·2%); the *picrate* was golden needles, m. p. 284° (decomp. >255°) (from ethanol) (Found: N, 14·5. $C_{23}H_{21}N_5O_7$ requires N, 14·6%).

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