Carcinogenic Nitrogen Compounds. Part LXXVI.[1] Penta- and Hexacyclic Indenoindoles

By **M. Dufour, N. P. Buu-Hoï,* P. Jacquignon,** and **D.-P. Hien,** Institut de Chimie des Substances Naturelles du C.N.R.S., 91-Gif-sur-Yvette, France

A number of new indenoindoles containing five or six rings have been prepared from acenaphthenone, angular naphthindanones, *s*-hydrindacen-1-one, and 2,3,4,6,7,8-hexahydro-1*H*-benz[*f*]inden-1-one, as potential carcinogens and enzyme inducers. Several of these compounds are highly potent inducers of zoxazolamine hydroxylase.

It has been found that benzindenoindoles [2] can exhibit carcinogenic properties; [3] more recently, strong enzyme-inducing [4] and photodynamic [5] activities have been discovered in this family of compounds. This paper reports the synthesis and properties of a number of penta- and hexa-cyclic compounds in this group.

[1] Part LXXV, N. P. Buu-Hoï, P. Jacquignon, D. C. Thang, and T. Bartnik, *J.S.C. Perkin I*, 1972, 263.

[2] N. P. Buu-Hoï, N. H. Khôi, and N. D. Xuong, *J. Org. Chem.*, 1951, **16**, 315; N. P. Buu-Hoï and N. D. Xuong, *J. Chem. Soc.*, 1952, 2225.

[3] A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, and N. D. Xuong, *Bull. Cancer*, 1955, **42**, 3.

[4] N. P. Buu-Hoï and D.-P. Hien, *Biochem. Pharmacol.*, 1968, **17**, 1227.

[5] S. S. Epstein, N. P. Buu-Hoï, and D.-P. Hien, *Cancer Res.*, 1971, **31**, 1087.

Whereas the various indenoindoles recorded in Table 1 were all synthesised smoothly and in high yield by Fischer indolisation (with a solution of hydrogen chloride in acetic acid) of the appropriate arylhydrazone, Korczynski *et al.*[6] in a similar way and assigned the same structure. Since a compound of m.p. 200° which the same authors prepared from acenaphthenone phenylhydrazone has now also been found to differ from

TABLE 1

New polycyclic indenoindoles [a]

			Found (%)			Required (%)		
Pentacyclic	M.p. (°C)	Formula	C	H	N	C	H	N
7,12-Dihydrobenz[4,5]indeno[1,2-*b*]indole (I)	275	$C_{19}H_{13}N$	89·3	5·3	5·4	89·4	5·1	5·5
2,3,5,10-Tetrahydro-1*H*-cyclopent[5,6]indeno[1,2-*b*]indole (II)	292	$C_{18}H_{15}N$	88·0	6·3	5·5	88·1	6·2	5·7
5,7,8,9,10,12-Hexahydrobenz[5,6]indeno[1,2-*b*]indole	280	$C_{19}H_{17}N$	88·1	6·7	5·6	88·0	6·6	5·4
5,12-Dihydrobenz[5,6]indeno[1,2-*b*]indole (III)	350 [c]	$C_{19}H_{13}N$	89·3	4·9	5·5	89·4	5·1	5·5
Hexacyclic								
7,14-Dihydrobenzo[*g*]benz[4,5]indeno[1,2-*b*]indole (IV)	350	$C_{23}H_{15}N$	90·3	5·0	4·4	90·5	5·0	4·6
7,14-Dihydrobenzo[*e*]benz[4,5]indeno[1,2-*b*]indole (V)	260	$C_{23}H_{15}N$	90·5	4·7	4·4	90·5	5·0	4·6
7,14-Dihydrobenzo[*g*]benz[6,7]indeno[1,2-*b*]indole (VI)	245	$C_{23}H_{15}N$	90·5	5·1	4·5	90·5	5·0	4·6
7,14-Dihydrobenzo[*e*]benz[6,7]indeno[1,2-*b*]indole (VII)	303	$C_{23}H_{15}N$	90·6	5·0	4·5	90·5	5·0	4·6
7,10,11,13-Tetrahydro-9*H*-benzo[*g*]cyclopent[5,6]indeno[1,2-*b*]-indole (VIII)	253	$C_{22}H_{17}N$	89·6	5·9	4·6	89·5	5·8	4·8
9,10,11,13-Tetrahydro-7*H*-benzo[*e*]cyclopent[5,6]indeno[1,2-*b*]-indole (IX)	240	$C_{22}H_{17}N$	89·7	5·8	4·8	89·5	5·8	4·8
7,9,10,11,12,14-Hexahydrobenzo[*g*]benz[5,6]indeno[1,2-*b*]-indole	220	$C_{23}H_{19}N$	89·3	6·2	4·4	89·3	6·2	4·5
7,14-Dihydrobenzo[*g*]benz[5,6]indeno[1,2-*b*]indole (X)	280 [c]	$C_{23}H_{15}N$	90·4	5·2	4·5	90·5	5·0	4·6
7,9,10,11,12,14-Hexahydrobenz[*e*]benz[5,6]indeno[1,2-*b*]indole	208	$C_{23}H_{19}N$	89·4	6·3	4·5	89·3	6·2	4·5
7,14-Dihydrobenzo[*e*]benz[5,6]indeno[1,2-*b*]indole (XI)	305 [c]	$C_{23}H_{15}N$	90·2	5·0	4·7	90·5	5·0	4·6
7*H*-Acenaphtho[1,2-*b*]benz[*g*]indole (XII) [b]	293	$C_{22}H_{13}N$	90·4	4·7	4·6	90·7	4·5	4·8
7*H*-Acenaphtho[1,2-*b*]benz[*e*]indole (XIII) [b]	270	$C_{22}H_{13}N$	90·9	4·3	4·8	90·7	4·5	4·8

[a] Crystallised from ethanol, cyclohexane, or benzene; all found colourless needles except the last two. [b] Orange leaflets (from benzene). [c] Obtained by dehydrogenation of the preceding compound by sublimation over 5% palladised charcoal.

TABLE 2

Significant chemical shifts (60 MHz) of protons in polycyclic indenoindoles

		τ Values			
Compound	Solvent	CH_2 (s)	NH (s)	Tertiary H	Aromatic H
(I) [a]	$(CD_3)_2SO$	6·00	−1·60		2·32 (m)
	$CF_3{\cdot}CO_2H$	6·00br (dd)		4·39 (d)	
(IV)	$(CD_3)_2SO$	6·00	−2·50		1·64 (dd, 8-H)
					2·17 (m, other protons)
(V)	$(CD_3)_2SO$	5·75	−2·00		2·17 (m)
(VI)	$(CD_3)_2SO$	6·14	−2·75		2·17 (m)
(VII)	$(CD_3)_2SO$	5·92	−2·33		2·17 (m)
(II) [b]	$CDCl_3$	6·63	1·75		2·28 (m)
(VIII)	$CDCl_3$	6·68	1·17		2·50 (m)
(IX)	$CDCl_3$	6·17	1·50		2·68 (m)
7,8,9,10-Tetrahydro- (III) [c]	$CDCl_3$	6·42	1·88		2·68 (m)
(III)	$(CD_3)_2SO$	6·14	−1·60		2·32 (m)
	$CF_3{\cdot}CO_2H$	6·33br (dd)		4·83	1·50 (s, 6-H)
9,10,11,12-Tetrahydro- (X) [d]	$CDCl_3$	6·63	1·00		2·68 (m)
(X)	$(CD_3)_2SO$	6·09	−2·50		2·17 (m)
9,10,11,12-Tetrahydro- (XI) [d]	$CDCl_3$	6·17	1·00		2·68
(XI)	$(CD_3)_2SO$	5·89	−2·10		2·17
(XII)	$(CD_3)_2SO$		−2·33		1·50 (dd, 8-H)
					2·17 (m, other protons)
(XIII) [e]	$(CD_3)_2SO$		−2·00		1·34 (dd, 13-H)
					1·75 (dd, 1-H)
					2·25 (m, other protons)

[a] For the isomeric 7,12-dihydrobenz[6,7]indeno[1,2-*b*]indole,[2] values ($CDCl_3$) were: τ 6·19 (CH_2), 1·34 (NH), 2·32 (m, aromatic); in $CF_3{\cdot}CO_2H$: τ 6·17br (dd, CH_2), 4·39 (d, tertiary H). [b] For CH_2 groups in cyclopentene ring, τ 7·00 (m) and 8·00 (m). [c] For CH_2 groups, τ 7·18 (m, 7- and 10-H_2) and 8·18 (m, 8- and 9-H_2). [d] For CH_2 groups, τ 7·18 (m, 9- and 12-H_2) and 8·18 (m), 10- and 11-H_2). [e] Signals (Me_2SO) for the known 7*H*-acenaphth[1,2-*b*]indole: τ −2·00 (NH) and 2·50 (m, other protons).

the preparation of the cyclic ketone starting materials merits comment in some cases, as does the structure of the indole obtained from acenaphthenone α-naphthylhydrazone. This last indole (XII), m.p. 293°, differed considerably from a compound of m.p. 256° prepared by authentic 7*H*-acenaphth[1,2-*b*]benz[*g*]indole,[7] m.p. 238° (lit.,[7] 235°), it is possible that the ketone they used either was impure or had another structure.

1,2-Dihydrobenz[*e*]inden-3-one and 2,3-dihydrobenz-[*e*]inden-1-one were readily prepared by the method of

[6] A. Korczynski, W. Brydowna, and L. Kierzek, *Gazzetta*, 1926, **56**, 903.

[7] A. C. Sircar and M. D. R. Gopalan, *J. Indian Chem. Soc.*, 1932, **9**, 297.

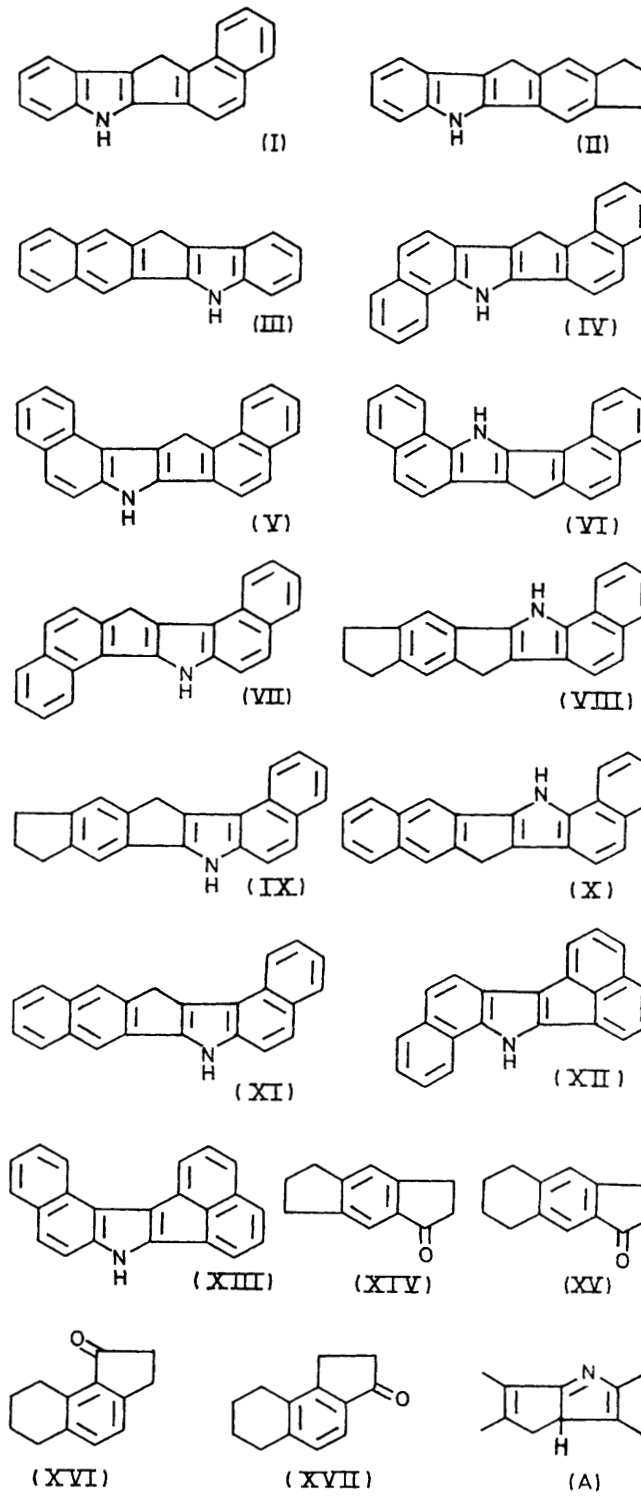
Baddeley *et al.*,[8] starting with a Friedel–Crafts acylation of naphthalene with maleic anhydride (which gave, in the same operation, the two required acryloylnaphthalenecarboxylic acids), and *s*-hydrindacen-1-one (XIV) was readily accessible from hydrindene and β-chloropropionyl chloride by means of Arnold's method[9] as simplified by Hart and Teble;[10] however, the synthesis of ketone (XV) free from its isomers (XVI) and (XVII) presented some difficulty. Friedel–Crafts acylation of tetralin afforded pure 6-(β-chloropropionyl)tetralin, but subsequent treatment with sulphuric acid led to a mixture of the two possible ketones (XV) and (XVII), which could however be resolved into its components *via* the semicarbazones. The alternative methods indicated in the literature, based on chloromethylation of tetralin followed by a malonic ester synthesis of the appropriate β-(tetralin-6-yl)propionic acid,* proved more tedious. We found (by g.l.c.) that the chloromethylation product of tetralin was an unresolvable mixture of 43% of the 5-isomer and 57% of the 6-isomer, with the result that the final product was a mixture of the three isomers (XV)—(XVII) [whereas β-(tetralin-5-yl)propionyl chloride underwent Friedel–Crafts cyclisation to give only (XVII), its 6-isomer afforded a mixture of only 45% of the desired ketone (XV) and 55% of (XVI)].

The n.m.r. spectra [solutions in both neutral ($CDCl_3$ or Me_2SO) and acidic ($CF_3{\cdot}CO_2H$) solvents] of the various indenoindoles (Table 2) display some interesting features, especially with reference to the chemical shifts of the methylene and imino-protons, which are highly sensitive to the deshielding influence of angular benzene rings; this supplies confirmation of the structures ascribed. In trifluoroacetic acid, as already found for similar indoles,[13] the NH signal disappears, probably through tautomeric conversion into the indolenine form (A), with appearance of the corresponding tertiary alicyclic proton signal.

All the penta- and hexa-cyclic indenoindoles tested were powerful inducers of the biosynthesis of the microsomal enzymatic system zoxazolamine hydroxylase in young rats (Table 3). As this activity is known to be present in the vast majority of polycyclic carcinogens,[4,14] these compounds are being examined for potential carcinogenicity and results will be published elsewhere.

EXPERIMENTAL

s-Hydrindacen-1-one (XIV).—Into a solution of hydrindene (20 g) and β-chloropropionyl chloride (22 g) in methylene chloride (200 ml), powdered aluminium chloride (25 g) was stirred during 1 h at 18°; the solvent was then distilled off, the cooled residue was treated dropwise with sulphuric acid (200 ml), and the mixture was heated at 90° for 1 h. After decomposition with ice and extraction of the product in ether, the ketone (b.p. 180° at 18 mmHg; m.p.



* Granger *et al.*[11] obtained ketones (XV) and (XVI) by this method, whereas Darzens and Levy[12] reported the formation of (XV) only.

[8] G. Baddeley, G. Hott, S. M. Makar, and M. G. Ivinson, *J. Chem. Soc.*, 1952, 3605.
[9] R. T. Arnold and E. Rondestvedt, *J. Amer. Chem. Soc.*, 1945, **67**, 1265.
[10] R. T. Hart and R. F. Teble, *J. Amer. Chem. Soc.*, 1950, **72**, 3286.
[11] R. Granger, H. Orzalisa, and A. Muratelle, *Bull. Soc. chim. France*, 1961, 1277.
[12] G. Darzens and A. Levy, *Compt. rend.*, 1935, **201**, 902.
[13] N. P. Buu-Hoï, V. Bellavita, G. Grandolini, A. Ricci, and P. Jacquignon, *Compt. rend.*, 1966, **262***C*, 1204.
[14] N. P. Buu-Hoï and D.-P. Hien, *Biochem. Pharmacol.*, 1969, **18**, 741.

80°) was purified by distillation *in vacuo* and recrystallisation from hexane; yield 60%.

1,2-*Dihydrobenz*[e]*inden*-3-*one and* 2,3-*Dihydrobenz*[e]*inden*-1-*one*.—These ketones, b.p. 185° at 18 mmHg, were prepared according to the literature,[8] the initial step, *i.e.* Friedel–Crafts condensation of maleic anhydride with naphthalene, being performed in methylene chloride, with 80—85% yield of the two isomeric β-naphthoylacrylic acids.

TABLE 3

Inducing effect of indenoindoles on zoxazolamine hydroxylase biosynthesis [a]

Compound	Duration of paralysis (min) [b,c] Pretreated [d]	Controls
(I)	20 ± 4(4)	204 ± 60(7)
(II)	30 ± 8(5)	435 ± 74(8)
(III)	23 ± 2(6)	373 ± 47(6)
(IV)	32 ± 8(6)	372 ± 80(6)
(V)	29 ± 7(6)	204 ± 60(7)
(VI)	27 ± 9(6)	204 ± 60(7)
(VII)	18 ± 6(6)	204 ± 60(7)
(VIII)	33 ± 10(5)	435 ± 74(8)
(IX)	42 ± 7(5)	435 ± 74(8)
Tetrahydro-(X)	43 ± 8(2)	435 ± 74(8)
(XI)	56 ± 13(5)	435 ± 74(8)
(XII)	23 ± 5(5)	372 ± 80(6)
(XIII)	21 ± 8(6)	372 ± 80(6)
7*H*-Acenaphth[1,2-*b*]indole	23 ± 5(5)	372 ± 80(6)

[a] Substance under test (20 mg per kg in corn oil) administered by intraperitoneal injection in young Wistar rats weighing *ca.* 100 g, 24 h prior to intraperitoneal injection of the paralysing drug zoxazolamine hydrochloride (90 mg per kg in saline). The controls received the paralysing drug alone. [b] Reduction in duration of paralysis parallels stimulation of zoxazolamine hydroxylase biosynthesis.[4] [c] Standard deviations given; figures in parentheses are numbers of rats. [d] $p < 0.001$ for all compounds tested.

2,3,5,6,7,8-*Hexahydro*-1H-*benz*[f]*inden*-1-*one* (XV).—Into a solution of tetralin (50 g) and β-chloropropionyl chloride (50 g) in methylene chloride (300 ml), aluminium chloride (60 g) was stirred during 3 h at 18°; after decomposition of the product with ice–hydrochloric acid, the organic layer was washed with water and dried (Na_2SO_4), the solvent was distilled off, and the oil obtained was purified by column chromatography on silica. 6-(β-*Chloropropionyl*)*tetralin* (eluted with benzene) formed leaflets (60 g), m.p. 62° (from hexane) (Found: C, 70·4; H, 6·8; Cl, 15·6. $C_{13}H_{15}ClO$ requires C, 70·1; H, 6·8; Cl, 15·9%). Cyclisation to a mixture (20 g) of ketones (XV) and (XVII) was affected by treatment with concentrated sulphuric acid (10 parts to 1 part of the chloro-ketone) at 90° for 1 h. The ketones were separated *via* the semicarbazones, that of (XV) being less soluble in butanol than its isomer. Hydrolysis of the semicarbazones with boiling dilute hydrochloric acid afforded ketone (XV) (11 g), b.p. 195° at 18 mmHg, m.p. 63°, and ketone (XVII) (10 g), b.p. 195° at 18 mmHg, m.p. 45°.

Chloromethylation of Tetralin.—This, performed as indicated by Arnold and Barnes,[15] gave a product, b.p. 140° at 11 mmHg, which n.m.r. measurements showed to be made up of 43% 5-chloromethyltetralin and 57% of the 6-isomer (Arnold and Barnes, using an elaborate chemical method, obtained 30% of the 5- and 70% of the 6-isomer). Authentic samples of each isomer were prepared from 5- and 6-hydroxymethyltetralin and thionyl chloride. 6-Hydroxymethyltetralin, b.p. 170° at 17 mmHg (1·8 g), was obtained from pure 6-formyltetralin (b.p. 155° at 13 mmHg; 3 g) [semicarbazone, m.p. 240° (lit.,[16] 228°)] by a Cannizzaro reaction with potassium hydroxide (4 g) and 30% aqueous formaldehyde (2 ml) in methanol (10 ml) at 60—70° (3 h). The 5-isomer was similarly obtained. The n.m.r. determination of the proportions of 5- and 6-chloromethyltetralin in the chloromethylation product of tetralin is based on the integration of the singlets (δ *ca.* 4·7 p.p.m.) corresponding to the CH_2Cl protons.

Preparation of Ketones (XV), (XVI), *and* (XVII) via '*Chloromethyltetralin*'.—The β-tetralinylpropionic acid prepared according to the literature [11] (10 g) could be cyclised either by polyphosphoric acid (80 g; 110° for 90 min; yield 8 g), or *via* the acid chloride [11] (yield 7 g), both methods giving a mixture of ketones (XV)—(XVII) which could be resolved *via* the semicarbazones [the semicarbazone of (XVI) was considerably more soluble in ethanol than those of (XV) and (XVII), which were separated from each other by crystallisation from butanol].

TABLE 4

M.p.s (°C) of arylhydrazones [a]

	(XIV)	1,2-Dihydrobenz[*e*]-inden-3-one	2,3-Dihydrobenz[*e*]-inden-1-one	(XV)	Acenaphthenone
Phenylhydrazone	127	170	160	141	90
α-Naphthylhydrazone	180	210	217	183	187
β-Naphthylhydrazone	168	205	212	145	151

[a] Crystallised from ethanol.

Preparation of Indenoindoles.—Indolisation of the arylhydrazones (m.p.s in Table 4) was effected by bringing to the boil a suspension of the hydrazone (1 part) in acetic acid saturated with hydrogen chloride (4—8 parts); the cooled mixture was diluted with water and the indenoindole obtained (in 80—95% yield) was washed thoroughly with water and crystallised.[17]

[1/1765 *Received, September 27th*, 1971]

[15] R. T. Arnold and R. Barnes, *J. Amer. Chem. Soc.*, 1943, **65**, 2393.

[16] C. L. Hewett, *J. Chem. Soc.*, 1938, 1286.

[17] Biological results presented (by P. J.) at the 1971 European Congress of Medicinal Chemistry (Lyons).