415. *Carcinogenic Nitrogen Compounds. Part XI.* Indeno(3′ : 2′-2 : 3)indoles, Benzindeno(3′ : 2′-2 : 3)indoles, and Related Compounds.*

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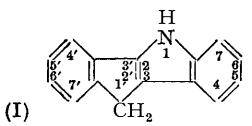
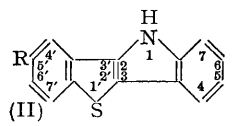
A number of indeno(3′ : 2′-2 : 3)indoles and their 4 : 5- and 6 : 7-benzo-analogues and similar compounds have been synthesised for their carcinogenic activity to be tested. Several 3-substituted derivatives of 4 : 5- and 6 : 7-benzindoles, considered as simpler models of the carcinogenic dibenzocarbazoles, have also been prepared. In the course of this research, a wide series of new 2-arylideneindan-1-ones and 2-arylidenebenzosuberones was obtained.

The versatile carcinogenic activity of benzocarbazoles and dibenzocarbazoles (Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429; Schürch and Winterstein, *Z. physiol. Chem.*, 1935, **236**, 79; Lacassagne, Buu-Hoï, Royer, and Zajdela, *Compt. rend. Soc. biol.*, 1947, **141**, 635) and their inhibitory effect on grafted tumours (Badger *et al.*, *Proc. Roy. Soc.*, 1942, *B*, **130**, 255) warrant the search for possible similar biological properties in structurally related nitrogenous heterocyclic compounds. The present work deals with compounds in the series of indeno(3′ : 2′-2 : 3)indole, one member of which, 4 : 5-benzindeno(3′ : 2′-2 : 3)indole, has already been found slightly carcinogenic (see Buu-Hoï, Hoán, and Khôi, *J. Org. Chem.*, 1950, **15**, 131); particular consideration has been given to the introduction of alkyl and halogen radicals.

Indeno(3′ : 2′-2 : 3)indole (I) itself was prepared by Hausmann (*Ber.*, 1889, **22**, 2021) by acid cyclisation of indan-1-one phenylhydrazone. Extension of this reaction to 6-methylindan-1-one *p*-tolylhydrazone and *p*-bromophenylhydrazone readily yielded the 5 : 5′-dimethyl and 5-bromo-5′-methyl derivatives; the lower homologue of the latter had already been prepared by Plant and Tomlinson (*J.*, 1931, 3324). 5′-*iso*Propyl-, 5′-chloro-,


(I)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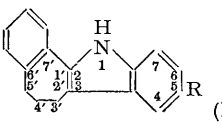
(III)

5′-chloro-5-methyl-, and 5-bromo-5′-chloro-indeno(3′ : 2′-2 : 3)indole were similarly prepared from the appropriate arylhydrazones of 6-*iso*propyl- and 6-chloro-indan-1-one; 5′-methylthianaphtheno(3′ : 2′-2 : 3)indole (II; R = Me), a compound structurally akin, was synthesised from 2 : 3-dihydro-3-keto-5-methylthianaphthen phenylhydrazone by the same reaction. Pentacyclic compounds included 4′ : 5′-benzindeno(3′ : 2′-2 : 3)indole, prepared by indolisation of 6 : 7-benzindan-1-one phenylhydrazone; on the other hand, indolisation of the α- and β-naphthylhydrazones of 6-methyl- and 6-chloroindan-1-one yielded 5′-methyl- and 5′-chloro-6 : 7-benzindeno(3′ : 2′-2 : 3)indole and 5′-methyl- and 5′-chloro-4 : 5-benzindeno(3′ : 2′-2 : 3)indole, respectively.

Indolisation of benzosuberone phenylhydrazone yielded 6′ : 7′-benzo*cyclo*heptadieno-(1′ : 2′-2 : 3)indole (III; R = H), a substance with the surprisingly low melting point of 98°, compared with that of indeno(3′ : 2′-2 : 3)indole (>247°); the corresponding 5-bromo-compound (III; R = Br) also melts at a considerably lower temperature than 5-bromo-indeno(3′ : 2′-2 : 3)indole; the melting points of the 6 : 7- and the 4 : 5-benzo-derivative of (III; R = H) are also remarkably low. These divergences are probably to be associated with the acidic character of the methylene group in indene derivatives, compared with the normal properties of those in benzo*cyclo*pentadieno-compounds.

As simpler models of 4 : 5- and 6 : 7-benzindeno(3′ : 2′-2 : 3)indole, 3-methyl-2-phenyl-4 : 5- and -6 : 7-benzindole were prepared by indolisation of propiophenone β- and α-naphthylhydrazone; 3-ethyl-2-phenyl- and 2-phenyl-3-*n*-propyl-4 : 5-benzindole, prepared from the β-naphthylhydrazones of propiophenone and *n*-butyrophenone, are similarly

* Part X, *J.*, 1952, 279.

simpler models of the carcinogenic 3 : 4-dihydro-1 : 2-5 : 6-dibenzocarbazole (this substance is slightly active in the production of sarcomas in subcutaneous injections; Lacassagne, Zajdela, Buu-Hoï, Hoán, and Xuong, *Bull. Cancer*, in the press) and of 4 : 5-6′ : 7′-dibenzo*cyclo*heptadieno(3′ : 2′-2 : 3)indole, respectively.

None of the above compounds tested has thus far produced tumours in mice.

During this research, various indan-1-ones and benzosuberones were condensed with aromatic aldehydes, furfuraldehyde, and thiophen aldehydes to give a series of new 2-arylideneindan-1-ones, 2-arylidenebenzosuberones, and similar compounds (for previous work on this subject see, *inter alia*, Kipping, *J.*, 1894, **65**, 269; Feuerstein, *Ber.*, 1901, **34**, 412; von Braun and Manz, *Annalen*, 1929, **468**, 258; Pfeiffer and Milz, *Ber.*, 1938, **71**, 272). These compounds, listed in the Tables, gave deep halochromic colours ranging from scarlet to violet, except for the derivatives of nitrated and halogenated benzaldehydes (hypsochromic effect of the halogen and nitro-groups) and of *p*-dimethylaminobenzaldehyde (" salt " effect).

Experimental

Preparation of Intermediates.—The various substituted indan-1-ones were prepared from the corresponding ring-substituted β-phenylpropionic acids, and the latter from the corresponding substituted benzyl chlorides, by conventional methods. 6-Ethylindan-1-one was characterised by its *semicarbazone*, crystallising from ethanol in fine, colourless prisms, m. p. 249° (Found : N, 19·2. $C_{12}H_{15}ON_3$ requires N, 19·4%); 4 : 6-*dimethylindan*-1-*one semicarbazone* formed from ethanol fine needles, m. p. 233° (Found : N, 19·3. $C_{12}H_{15}ON_3$ requires N, 19·4%); 6-iso*propylindan*-1-*one semicarbazone* formed from ethanol fine prisms, m. p. 232° (Found : N, 18·2. $C_{13}H_{17}ON_3$ requires N, 18·2%).

5 : 5′-*Dimethylindeno*(3′ : 2′-2 : 3)*indole.*—A mixture of *p*-tolylhydrazine hydrochloride (2 g.), 6-methylindan-1-one (1·5 g.), and sodium acetate (3 g.) was heated in ethanol for 30 minutes, and the *p*-tolylhydrazone formed on addition of water was collected and converted into the indole in the crude state by 2 minutes' boiling of its solution in acetic acid saturated with hydrogen chloride. The precipitate obtained (80% yield) by pouring the mixture into water crystallised from toluene as sublimable, colourless needles, m. p. 231° (Found : C, 87·5; H, 6·6. $C_{17}H_{15}N$ requires C, 87·5; H, 6·4%), giving a yellow colour with sulphuric acid, and a

Arylidene group	M. p.	Formula	Colour with H_2SO_4	Found, % C	Found, % H	Reqd., % C	Reqd., % H
2-Arylideneindan-1-ones.							
2-Thenylidene	157°	$C_{14}H_{10}OS$	Blood-red	74·2	4·7	74·3	4·4
2 : 5-Dimethyl-3-thenylidene	172	$C_{16}H_{14}OS$	Crimson-red	75·2	5·5	75·6	5·5
2-Chlorobenzylidene	158	$C_{16}H_{11}OCl$	Yellow	75·4	4·6	75·4	4·3
4-Chlorobenzylidene	179	$C_{16}H_{11}OCl$	Yellow	75·1	4·6	75·4	4·3
2 : 4-Dichlorobenzylidene	210	$C_{16}H_{10}OCl_2$	Yellow	66·2	3·4	66·4	3·5
3 : 4-Dichlorobenzylidene	193	$C_{16}N_{10}OCl_2$	Yellow	66·2	3·6	66·4	3·5
3 : 4-Dimethoxybenzylidene	177	$C_{18}H_{16}O_3$	Violet-red	77·4	5·5	77·1	5·7
1-Naphthylmethylene	130	$C_{20}H_{14}O$	Violet-red	88·5	5·5	88·9	5·2
5-Acenaphthylidene	227	$C_{22}H_{16}O$	Dark violet	89·0	5·6	89·2	5·5
3-Pyrenylidene	229	$C_{26}N_{16}O$	Dark violet	90·4	4·8	90·7	4·7
2-Arylidene-6-methylindan-1-ones.							
2-Furfurylidene	133°	$C_{15}H_{12}O_2$	Red	80·2	5·6	80·4	5·4
2-Thenylidene	179	$C_{15}H_{12}OS$	Blood-red	74·9	5·2	75·0	5·0
2-Chlorobenzylidene	160	$C_{17}H_{13}OCl$	Deep yellow	75·8	4·9	76·0	4·8
4-Chlorobenzylidene	212	$C_{17}H_{13}OCl$	Yellow	75·9	4·9	76·0	4·8
2 : 4-Dichlorobenzylidene	210	$C_{17}H_{12}OCl_2$	Canary-yellow	67·1	4·0	67·3	3·9
3 : 4-Dichlorobenzylidene	181	$C_{17}H_{12}OCl_2$	Canary-yellow	67·2	4·1	67·3	3·9
4-Dimethylaminobenzylidene	154	$C_{19}H_{19}ON$	Yellow	82·0	6·7	82·3	6·9
3-Nitrobenzylidene	142	$C_{17}N_{13}O_3N$	Deep yellow	73·0	4·9	73·1	4·7
2-Methoxybenzylidene	134	$C_{18}H_{16}O_2$	Blood-red	81·5	6·4	81·8	6·1
4-Methoxybenzylidene	111	$C_{18}H_{16}O_2$	Blood-red	81·5	6·2	81·8	6·1
3 : 4-Dimethoxybenzylidene	170	$C_{19}H_{18}O_3$	Purple-red	77·8	6·0	77·6	6·1
Piperonylidene	168	$C_{18}H_{14}O_3$	Blood-red	77·6	5·2	77·7	5·0
1-Naphthylmethylene	150	$C_{21}H_{16}O$	Deep red	88·3	5·5	88·7	5·6
2-Naphthylmethylene	206	$C_{21}H_{16}O$	Deep red	88·2	5·4	88·7	5·6
2-Methoxy-1-naphthylmethylene	133	$C_{22}H_{18}O_2$	Deep violet	84·4	5·4	84·1	5·7
5-Acenaphthylidene	194	$C_{23}H_{18}O$	Deep violet	88·9	5·9	89·0	5·8
3-Pyrenylidene	201	$C_{27}H_{18}O$	Deep violet	90·2	5·2	90·5	5·0

Arylidene group	M. p.	Formula	Colour with H_2SO_4	Found, % C	Found, % H	Reqd., % C	Reqd., % H
2-Arylidene-6-ethylindan-1-ones.							
3 : 4-Dimethoxybenzylidene	150°	$C_{20}H_{20}O_3$	Blood-red	77·6	6·8	77·9	6·5
4-Chlorobenzylidene	175	$C_{18}H_{15}OCl$	Orange-yellow	76·3	5·3	76·5	5·3
2 : 4-Dichlorobenzylidene	178	$C_{18}H_{14}OCl_2$	Yellow	67·8	4·4	68·1	4·4
3 : 4-Dichlorobenzylidene	166	$C_{18}H_{14}OCl_2$	Yellow	68·0	4·6	68·1	4·4
3-Nitrobenzylidene	182	$C_{18}H_{15}O_3N$	Canary-yellow	73·5	5·0	73·7	5·1
4-Dimethylaminobenzylidene	146	$C_{20}H_{21}ON$	Canary-yellow	82·2	7·2	82·5	7·2
5-Acenaphthylidene	196	$C_{24}H_{20}O$	Deep violet	88·6	6·4	88·9	6·2
2-Arylidene-6-isopropylindan-1-ones.							
4-Chlorobenzylidene	142°	$C_{19}H_{17}OCl$	Orange-yellow	76·6	5·8	76·9	5·7
3 : 4-Dichlorobenzylidene	196	$C_{19}H_{16}OCl_2$	Yellow	68·8	4·9	68·9	4·8
3-Nitrobenzylidene	199	$C_{19}H_{17}O_3N$	Canary-yellow	74·0	5·7	74·3	5·5
4-Dimethylaminobenzylidene	157	$C_{21}H_{23}ON$	Canary-yellow	82·4	7·4	82·6	7·5
5-Acenaphthylidene	213	$C_{25}H_{22}O$	Deep violet	88·9	6·4	88·8	6·5
2-Arylidene-6-chloroindan-1-ones.							
4-Dimethylaminobenzylidene	202°	$C_{18}H_{16}ONCl$	Yellow	72·2	5·5	72·6	5·4
2-Methoxybenzylidene	177	$C_{17}H_{13}O_2Cl$	Blood-red	71·5	4·8	71·7	4·6
4-Methoxybenzylidene	202	$C_{17}H_{13}O_2Cl$	Blood-red	71·6	4·4	71·7	4·6
2-Chlorobenzylidene	227	$C_{16}H_{10}OCl_2$	Deep yellow	66·1	3·8	66·4	3·5
4-Chlorobenzylidene	260	$C_{16}H_{10}OCl_2$	Yellow	66·3	3·6	66·4	3·5
2 : 4-Dichlorobenzylidene	255	$C_{16}H_9OCl_3$	Yellow	59·1	3·0	59·4	2·8
3 : 4-Dichlorobenzylidene	215	$C_{16}H_9OCl_3$	Yellow	59·3	3·0	59·4	2·8
3 : 4-Dimethoxybenzylidene	195	$C_{18}H_{15}O_3Cl$	Blood-red	68·4	5·1	68·7	4·8
Piperonylidene	235	$C_{17}H_{11}O_3Cl$	Violet-red	68·0	3·8	68·3	3·7
1-Naphthylmethylene	168	$C_{20}H_{13}OCl$	Vermilion-red	78·7	4·1	78·8	4·3
2-Naphthylmethylene	203	$C_{20}H_{13}OCl$	Vermilion-red	78·5	4·1	78·8	4·3
5-Acenaphthylidene	235	$C_{22}H_{15}OCl$	Deep violet	80·0	4·7	79·9	4·5
3-Pyrenylidene	281	$C_{26}H_{15}OCl$	Deep violet	82·2	4·1	82·4	4·0
2-Arylidene-4 : 6-dimethylindan-1-ones.							
4-Dimethylaminobenzylidene	208°	$C_{20}H_{21}ON$	Yellow	84·2	6·4	84·4	6·6
3 : 4-Dimethoxybenzylidene	176	$C_{20}H_{20}O_3$	Blood-red	79·8	6·1	79·9	5·9
Piperonylidene	214	$C_{19}H_{16}O_3$	Violet-red	78·0	4·5	78·1	4·7
2-Chlorobenzylidene	202	$C_{18}H_{15}OCl$	Deep yellow	76·2	5·2	76·5	5·3
4-Chlorobenzylidene	192	$C_{18}H_{15}OCl$	Yellow	76·3	5·1	76·5	5·3
2 : 4-Dichlorobenzylidene	195	$C_{18}H_{14}OCl_2$	Pale yellow	67·9	4·4	68·1	4·4
3 : 4-Dichlorobenzylidene	215	$C_{18}H_{14}OCl_2$	Pale yellow	68·0	4·2	68·1	4·4
4-Methoxybenzylidene	157	$C_{19}H_{18}O_2$	Blood-red	81·7	6·8	82·0	6·5
2-Naphthylmethylene	199	$C_{22}H_{18}O$	Blood-red	88·8	6·2	88·6	6·0
5-Acenaphthylidene	214	$C_{24}H_{20}O$	Deep violet	88·8	6·0	88·9	6·2
3-Pyrenylidene	228	$C_{28}H_{20}O$	Deep violet	90·0	5·2	90·3	5·4
2-Arylidenebenzosuberones.							
4-Dimethylaminobenzylidene	176°	$C_{20}H_{21}ON$	Yellow	82·2	7·1	82·5	7·2
4′-Chlorobenzylidene	88	$C_{18}H_{15}OCl$	Orange-yellow	76·2	5·1	76·5	5·3
2 : 4-Dichlorobenzylidene	136	$C_{18}H_{14}OCl_2$	Orange-yellow	68·0	4·4	68·1	4·4
3-Nitrobenzylidene	116	$C_{18}H_{15}O_3N$	Yellow	73·4	5·4	73·7	5·1
4′-Methoxybenzylidene	111	$C_{19}H_{18}O_2$	Blood-red	81·8	6·4	82·0	6·5
Piperonylidene	138	$C_{19}H_{16}O_3$	Blood-red	78·0	5·2	78·1	5·5
1-Naphthylmethylene	96	$C_{22}H_{18}O$	Vermilion-red	88·3	6·2	88·6	6·0
2-Methoxy-1-naphthylmethylene	129	$C_{23}H_{20}O_2$	Deep violet	84·0	6·4	84·1	6·1
3-Pyrenylidene	160	$C_{28}H_{20}O$	Violet-blue	90·0	5·2	90·3	5·4
3 : 4-Dichlorobenzylidene	110	$C_{18}H_{14}OCl_2$	Orange-yellow	67·8	4·6	68·1	4·4

violet picrate; *5-bromo-5′-methylindeno*(3′ : 2′-2 : 3)*indole* formed from benzene fine colourless prisms, m. p. 199—200°, giving also a violet picrate and with sulphuric acid a yellow colour (Found: C, 64·1; H, 4·1. $C_{16}H_{12}NBr$ requires C, 64·4; H, 4·0%); 5′-iso*propylindeno*(3′ : 2′-2 : 3)*indole* was purified by vacuum-distillation (b. p. 265°/15 mm.), and crystallised from acetic acid in fine, colourless prisms, m. p. 170° (Found: N, 5·6. $C_{18}H_{17}N$ requires N, 5·7%); *5′-chloroindeno*(3′ : 2′-2 : 3)*indole*, obtained from 6-chloroindan-1-one (von Miller and Rohde, *Ber.*, 1890, **23**, 1887; Kenner and Witham, *J.*, 1921, **119**, 1452), formed from toluene colourless, sublimable leaflets, m. p. 215° (Found: C, 75·0; H, 4·0. $C_{15}H_{10}NCl$ requires C, 75·1; H, 4·2%); its *5-methyl* derivative formed from xylene colourless leaflets, m. p. 278° (Found: N, 5·2. $C_{16}H_{12}NCl$ requires N, 5·5%); *5-bromo-5′-chloroindeno*(3′ : 2′-2 : 3)*indole* crystallised from benzene as shiny, colourless leaflets, m. p. 256° (Found: C, 56·4; H, 2·6. $C_{15}H_9NBrCl$ requires C, 56·5; H, 2·8%).

5′-*Methyl*(3′ : 2′-2 : 3)*thianaphthenoindole* formed from benzene yellowish needles, m. p. 208°, giving with sulphuric acid a violet colour (Found : C, 75·6; H, 4·8. $C_{15}H_{11}NS$ requires C, 75·9; H, 4·6%).

4′ : 5′-*Benzindeno*(3′ : 2′-2 : 3)*indole*.—The 6 : 7-benzindan-1-one used was prepared by aluminium chloride-cyclisation of 2-β-naphthylpropionyl chloride, and had m. p. 102°; the *indenoindole*, obtained in 90% yield, formed from ethanol pale yellow prisms, m. p. 210°, giving with sulphuric acid a blood-red colour (Found : C, 89·3; H, 5·2. $C_{19}H_{13}N$ requires C, 89·4; H, 5·1%).

5′-*Methyl*-6 : 7-*benzindeno*(3′ : 2′-2 : 3)*indole* formed colourless needles (from benzene; yield, 70%), m. p. 227—228°, giving with sulphuric acid a deep yellow colour (Found : N, 5·3. $C_{20}H_{15}N$ requires N, 5·2%); the corresponding 5′-*chloro*-compound crystallised from xylene as shiny, colourless needles (yield 60%), m. p. 208° (Found : C, 79·0; H, 4·0. $C_{19}H_{12}NCl$ requires C, 78·8; H, 4·1%).

5′-*Methyl*-4 : 5-*benzindeno*(3′ : 2′-2 : 3)*indole* formed colourless needles (from benzene; yield, 80%), m. p. 238°, giving with sulphuric acid a yellow colour (Found : C, 89·0; H, 5·8. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6%); the 5′-*chloro*-analogue separated from toluene as shiny, colourless needles, m. p. 205° (Found : C, 78·6; H, 4·2. $C_{19}H_{12}NCl$ requires C, 78·9; H, 4·1%).

6′ : 7′-*Benzo*cyclo*heptadieno*(1′ : 2′-2 : 3)*indole* formed colourless leaflets, highly soluble in benzene, m. p. 98°, giving with sulphuric acid a yellow colour (Found : C, 87·4; H, 6·2. $C_{17}H_{15}N$ requires C, 87·5; H, 6·4%); the picrate formed from benzene dark violet needles, m. p. 143°. The 5-*bromo*-derivative formed from benzene colourless leaflets, m. p. 130° (Found : C, 65·2; H, 4·4. $C_{17}H_{14}NBr$ requires C, 65·4; H, 4·5%), giving a dark violet picrate, m. p. 143°.

6 : 7-6′ : 7′-*Dibenzo*cyclo*heptadieno*(1′ : 2′-2 : 3)*indole* formed fine, grey-tinged prisms (from methanol), m. p. 103° (Found : C, 89·1; H, 6·0. $C_{21}H_{17}N$ requires C, 89·0; H, 6·0%), giving a dark violet picrate, m. p. 171° (from benzene); the isomeric 4 : 5-6′ : 7′-*dibenzo*-compound crystallised from benzene as colourless needles, m. p. 156° (Found : C, 88·8; H, 6·2%).

2 : 3-*Disubstituted* 4 : 5- *and* 6 : 7-*Benzindoles*.—Indoles in this series were obtained in good yields in the usual way by means of an acetic acid solution of hydrogen chloride (cf. Buu-Hoï, *J.*, 1949, 2882). 3-*Methyl*-2-*phenyl*-4 : 5-*benzindole* formed from methanol fine colourless needles, m. p. 147° (Found : C, 88·8; H, 5·6. $C_{19}H_{15}N$ requires C, 88·7; H, 5·8%), giving a violet picrate, m. p. 161° (from benzene); 3-*methyl*-2-*phenyl*-6 : 7-*benzindole* formed from ligroin fine, colourless needles, m. p. 117° (Found : C, 89·0; H, 5·7%), giving a violet picrate, m. p. 166°; 3-*ethyl*-2-*phenyl*-4 : 5-*benzindole* crystallised from methanol as silky, colourless needles, m. p. 126° (Found : C, 88·3; H, 6·6. $C_{20}H_{17}N$ requires C, 88·6; H, 6·3%); 2-*phenyl*-3-n-*propyl*-4 : 5-*benzindole* was extremely soluble in the usual solvents, and had m. p. 85—86° (from light petroleum, b. p. 40—60°) (Found : C, 88·2; H, 7·0. $C_{21}H_{19}N$ requires C, 88·3; H, 6·7%).

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