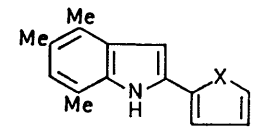
Carcinogenic Nitrogen Compounds. Part LXXXII.[1] Polycyclic Indoles by Means of the Möhlau–Bischler Synthesis

By P. Bigot, G. Saint-Ruf,* and (the late) N. P. Buu-Hoï,† Centre Marcel Délépine du C.N.R.S., 45-Orléans-La Source, France

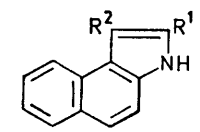
A modified technique for the Möhlau-Bischler indole synthesis gave access to a number of polycyclic indoles, among them derivatives of benzo[*f*]indole and phenaleno[1,9-*fg*]indole, which are potential carcinogens and/or leukaemogens.

We have recently shown[2] that the Möhlau–Bischler synthesis (*i.e.* cyclisation of ω-arylamino-ketones in the presence of arylamine salts) is an excellent preparative route to 2-arylindoles. This reaction has now been used for the preparation of a number of new polysubstituted indoles and polynuclear indoles which are of interest as potential carcinogenic and/or leukaemogenic substances; indole itself and some of its more simple substituted derivatives are known to induce leukaemia in rodents.[3]

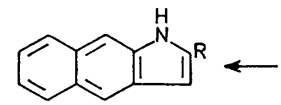
Since the Möhlau–Bischler method does not involve the use of metal halides as catalysts, the introduction of fragile heteroaromatic substituents presented no problems: thus, the 2-furyl (I; X = O) and 2-thienyl (I; X = S) derivatives of 4,5,7-trimethylindole were easily obtained from 2,4,5-trimethylaniline (pseudocumidine) and the appropriate ω-bromo-ketone, and the corresponding 2-pyridyl derivative was prepared similarly.



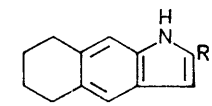
(I)



(II)



(III)



(IV)

A further advantage of the Möhlau–Bischler cyclisation is that there is no risk of isomerisation through methyl

† Deceased, 28th January, 1972.

[1] Part LXXXI, D. C. Thang, C. X. Can, N. P. Buu-Hoï, and P. Jacquignon, *J.C.S. Perkin I*, 1972, 1932.

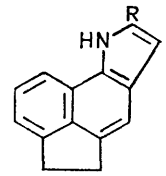
[2] N. P. Buu-Hoï, G. Saint-Ruf, D. Deschamps, and P. Bigot, *J. Chem. Soc.* (*C*), 1971, 2606.

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

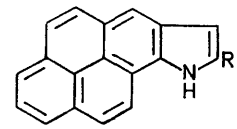
displacement, as demonstrated by analysis of the n.m.r. spectral data of a number of indoles derived from pseudocumidine; all the spectra showed a signal (τ 3·18—3·28) corresponding to the 6-proton shielded by the two adjacent methyl groups.

α-Arylaminodeoxybenzoins [4] proved particularly prone to indolisation; 4,5,7-trimethyl-2,3-diphenylindole and 1,2-diphenyl-3*H*-benz[*e*]indole (II; $R^1 = R^2 = Ph$) were furnished in excellent yield.[5] Other derivatives of 3*H*-benz[*e*]indole were prepared; the properties of the 2-phenyl derivative (m.p. 175°) differed considerably from those indicated in the literature.[6] A route to derivatives of 1*H*-benz[*f*]indole (III; R = H) involved use of 6-aminotetralin in Möhlau–Bischler syntheses; cyclisation of the ω-amino-ketones derived from this amine takes place at position 7 and thus gives substituted 5,6,7,8-tetrahydro-1*H*-benz[*f*]indoles (IV), which are then dehydrogenated to (III). Proof of the linear structure of these compounds was provided by the fact that the 2-phenyl derivative (III; R = Ph), m.p. 260°, displayed different physico-chemical properties from those of 2-phenyl-3*H*-benz[*e*]indole; furthermore, all the derivatives (IV) showed an intense i.r. absorption band in the 800—850 cm^{-1} region, characteristic of a 1,2,4,5-tetrasubstituted benzene and hence of the absence of *ortho*-related protons.[7]

The Möhlau–Bischler synthesis was also successfully applied to the cyclisation of ω-arylamino-ketones derived from 5-aminoacenaphthene and 1-aminopyrene, leading, respectively, to 8-aryl-5,9-dihydro-4*H*-indeno-[1,7-*fg*]indoles (V) and 8-aryl-9*H*-phenaleno[1,9-*fg*]indoles (VI). Compounds (VI) are particularly interesting in view of their close structural relationship with benzo[*a*]pyrene, one of the most potent carcinogens known.

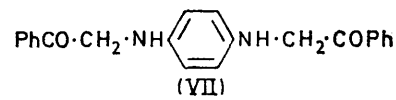


(V)

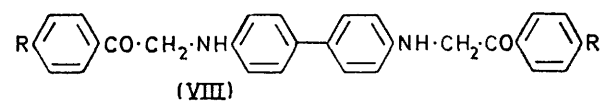


(VI)

Whilst aromatic diamines such as *p*-diaminobenzene and benzidine could be easily cyclised to the corresponding ω-amino-ketones (VII) and (VIII), similar cyclisation of these last compounds furnished only unidentified polymerisation products. Nevertheless, the many examples of the formation of indoles reported here show, in line with our earlier observations,[2] that the



(VII)



(VIII)

TABLE 1

ω-Arylamino-ketones,[a] ArNH·CHR·COAr'

Substituents					Found (%)			Requires (%)		
Ar	Ar'	R	M.p. (°C)	Formula	C	H	N	C	H	N
2,4-Xylyl	Ph	Ph	125	$C_{22}H_{21}NO$	83·5	6·7	4·2	83·7	6·7	4·4
3,4-Xylyl	Ph	Ph	126	$C_{22}H_{21}NO$	83·5	6·7	4·2	83·7	6·7	4·4
3,5-Xylyl	Ph	Ph	134	$C_{22}H_{21}NO$	83·6	6·7	4·2	83·7	6·7	4·4
2,3-Xylyl	Ph	Ph	115	$C_{22}H_{21}NO$	83·7	6·7	4·2	83·7	6·7	4·4
2,4,5-$Me_3C_6H_2$	Ph	Ph	138	$C_{23}H_{23}NO$	83·8	7·0	4·0	83·8	7·0	4·2
2-Naphthyl	Ph	H	155	$C_{18}H_{15}NO$	82·8	5·9	5·6	82·7	5·8	5·4
2-Naphthyl	ClC_6H_4	H	194	$C_{18}H_{14}ClNO$	72·9	5·0	4·9	73·1	4·8	4·7
2-Naphthyl	Biphenyl-4-yl	H	190	$C_{24}H_{19}NO$	85·4	5·9	4·0	85·4	5·7	4·1
5,6,7,8-Tetrahydro-2-naphthyl	Ph	H	135	$C_{18}H_{19}NO$	81·3	7·1	5·4	81·5	7·2	5·3
5,6,7,8-Tetrahydro-2-naphthyl	Ph	Ph [b]	130	$C_{24}H_{23}NO$	84·4	6·9	3·9	84·4	6·8	4·1
5,6,7,8-Tetrahydro-2-naphthyl	Biphenyl-4-yl	H	120	$C_{24}H_{23}NO$	84·3	6·9	3·9	84·4	6·8	4·1
5,6,7,8-Tetrahydro-2-naphthyl	*p*-ClC_6H_4	H	140	$C_{18}H_{18}ClNO$	71·9	6·0	4·6	72·1	6·0	4·7
5-Acenaphthyl	Ph	H	164	$C_{20}H_{17}NO$	83·5	6·0	5·0	83·6	6·0	4·9
5-Acenaphthyl	Ph	Me [c]	153	$C_{21}H_{17}NO$	83·6	6·4	4·6	83·7	6·3	4·6
5-Acenaphthyl	*p*-ClC_6H_4	H [d]	175	$C_{20}H_{16}ClNO$	74·7	5·1	4·1	74·6	5·0	4·3
5-Acenaphthyl	2-Naphthyl	H [b]	173	$C_{24}H_{19}NO$	85·2	5·8	4·1	85·4	5·7	4·2
5-Acenaphthyl	Biphenyl-4-yl	H [b]	188	$C_{26}H_{21}NO$	85·9	5·8	3·6	85·9	5·8	3·8
5-Acenaphthyl	Indan-5-yl	H [b]	178	$C_{23}H_{21}NO$	84·2	6·5	4·1	84·4	6·5	4·3
5-Acenaphthyl	*p*-MeO·C_6H_4	H [b]	145	$C_{21}H_{19}NO_2$	79·3	6·0	4·2	79·5	6·0	4·4
5-Acenaphthyl	2-Thienyl	H [b]	150	$C_{18}H_{15}NOS$	73·6	5·2	4·5	73·7	5·1	4·7
Pyren-1-yl	Ph	H [b]	162	$C_{24}H_{17}NO$	85·8	5·3	4·0	85·9	5·1	4·2
Pyren-1-yl	*p*-ClC_6H_4	H [b]	186	$C_{24}H_{16}ClNO$			3·7			3·8

[a] Pale yellow needles, from ethanol or ethanol–benzene. [b] From benzene. [c] From methanol. [d] From propanol.

[4] *Cf.* R. C. Elderfield, 'Heterocyclic Compounds,' Wiley, New York, 1952, vol. 3, p. 3.
[5] A. Bischler and P. Fireman, *Ber.*, 1893, **26**, 1346.
[6] W. H. Ince, *Annalen*, 1889, **253**, 35.
[7] *Cf.*, L. J. Bellamy, 'The Infrared Spectra of Complex Molecules,' Methuen, London, 1958; R. N. Jones and C. Sandorfy, in 'Techniques of Organic Chemistry,' ed. A. Weissberger, Interscience, New York, 1956, vol. IX; D. G. O'Sullivan, *Spectrochim. Acta*, 1960, **16**, 762.

Möhlau–Bischler synthesis is far superior to that of Fischer for the preparation of polycyclic 2-arylindoles.

EXPERIMENTAL

I.r. absorption spectra were determined for potassium bromide discs with a Perkin-Elmer (model 457) spectrometer; n.m.r. data were determined for solutions in [^{2}H]chloroform (internal reference, tetramethylsilane) with a Perkin-Elmer R-12 spectrometer.

Preparation of ω-Arylamino-ketones.—An ethanolic solution of equimolar amounts of the arylamine and the appropriate ω-bromo-ketone was heated under reflux for 4 h with hydrogen sodium carbonate in slight excess. The solution was cooled and the precipitate was washed with water and recrystallised from ethanol, ethanol–benzene, or benzene; yields 60—85% (see Table 1).

Möhlau–Bischler Cyclisation.—We used our modified technique,[2] the cyclisation being performed in an inert liquid (silicone oil), which avoids thermal decomposition of the ω-amino-ketones and gives higher yields of indoles. An intimate mixture of the ω-arylamino-ketone, the appropriate arylamine (2 mol. equiv.) and its hydrobromide (0·05 mol. equiv.) in silicone oil was heated at 230—250° for 10—15 min. The mixture was cooled and the product was washed with hexane and recrystallised from ethanol, benzene, or chlorobenzene; yields 35—80% (see Tables 2 and 3).

TABLE 2

Polysubstituted indoles

Indoles [a]	M.p. (°C)	Formula	Found (%) C	H	N	Requires (%) C	H	N
5,7-Dimethyl-2,3-diphenyl-	152	$C_{22}H_{19}N$	88·6	6·5	4·5	88·8	6·4	4·7
Picrate	163	$C_{28}H_{22}N_4O_7$	63·8	4·3	10·5	63·8	4·2	10·6
4,7-Dimethyl-2,3-diphenyl-	135	$C_{22}H_{19}N$	88·8	6·5	4·5	88·8	6·4	4·7
Picrate	142	$C_{28}H_{22}N_4O_7$	63·5	4·4	10·9	63·8	4·2	10·6
5,6-Dimethyl-2,3-diphenyl-	155	$C_{22}H_{19}N$	88·5	6·5	4·5	88·8	6·4	4·7
Picrate	160	$C_{28}H_{22}N_4O_7$	63·7	4·2	10·3	63·8	4·2	10·6
4,5-Dimethyl-2,3-diphenyl-	135	$C_{22}H_{19}N$	88·5	6·4	4·6	88·8	6·4	4·7
6,7-Dimethyl-2,3-diphenyl-	145	$C_{22}H_{19}N$	88·8	4·6	4·6	88·8	6·4	4·7
Picrate	167	$C_{28}H_{22}N_4O_7$	63·5	4·4	10·8	63·8	4·2	10·6
4,5,7-Trimethyl-2,3-diphenyl-	170	$C_{23}H_{21}N$	88·5	6·9	4·3	88·7	6·8	4·5

[a] Recrystallised from ethanol, aqueous ethanol, or hexane, as colourless leaflets or prisms. Picrates crystallised from ethanol, as brown needles.

TABLE 3

Polycyclic indoles [a]

	M.p. (°C)	Formula	Found (%) C	H	N	Requires (%) C	H	N
2-Phenyl-3*H*-benz[*e*]indole (II; R^1 = Ph, R^2 = H)	175	$C_{18}H_{19}N$	89·0	5·5	5·6	88·8	5·4	5·7
2-(*p*-Chlorophenyl)-3H-benz[*e*]indole (II; R^1 = *p*-ClC$_6$H$_4$, R^2 = H)	159	$C_{18}H_{12}ClN$	78·0	4·5	4·9	77·8	4·4	5·0
2-(Biphenyl-4-yl)-3*H*-benz[*e*]indole (II; R^1 = *p*-C$_6$H$_5$·C$_6$H$_4$, R^2 = H)	245	$C_{24}H_{17}N$	89·9	5·5	4·5	90·2	5·4	4·4
5,6,7,8-Tetrahydro-2-phenyl-1*H*-benz[*f*]indole (IV; R = Ph)	201	$C_{18}H_{17}N$	87·2	7·0	5·6	87·4	6·9	5·7
2-(*p*-Chlorophenyl)-5,6,7,8-tetrahydro-1*H*-benz[*f*]indole (IV; R = *p*-ClC$_6$H$_4$)	276	$C_{18}H_{16}ClN$	76·6	5·8	4·8	76·7	5·7	4·9
2-(Biphenyl-4-yl)-5,6,7,8-tetrahydro-1*H*-benz[*f*]indole (IV; R = *p*-C$_6$H$_5$·C$_6$H$_4$)	305	$C_{24}H_{21}N$	89·3	6·5	4·1	89·1	6·5	4·3
2-Phenyl-1*H*-benz[*f*]indole (III; R = Ph)	260	$C_{18}H_{13}N$	88·6	5·4	5·8	88·8	5·4	5·7
5,9-Dihydro-8-phenyl-4*H*-indeno[1,7-*fg*]indole (V; R = Ph)	164	$C_{20}H_{15}N$	89·1	5·6	5·0	89·2	5·6	5·2
Picrate	201	$C_{26}H_{18}N_4O_7$	62·6	3·7	10·9	62·7	3·7	11·2
8-(*p*-Chlorophenyl)-5,9-dihydro-4*H*-indeno[1,7-*fg*]indole (V; R = *p*-ClC$_6$H$_4$)	190	$C_{20}H_{14}ClN$	78·9	4·8	4·5	79·1	4·6	4·6
Picrate	185	$C_{26}H_{17}ClN_4O_7$	58·3	3·2	10·3	58·6	3·2	10·5
8-(β-Naphthyl)-5,9-dihydro-4*H*-indeno[1,7-*fg*]indole (V; R = β-naphthyl)	197	$C_{24}H_{17}N$	89·9	5·5	4·2	90·2	5·4	4·4
Dipicrate	214	$C_{36}H_{23}N_7O_{14}$	55·8	3·1	12·5	55·6	3·0	12·6
8-(Biphenyl-4-yl)-5,9-dihydro-4*H*-indeno[1,7-*fg*]indole (V; R = *p*-C$_6$H$_5$·C$_6$H$_4$)	260	$C_{26}H_{19}N$	90·4	5·6	3·8	90·4	5·5	4·0
Picrate	200	$C_{32}H_{22}N_4O_7$	66·6	3·9	9·8	66·8	3·7	9·7
8-(Indan-5-yl)-5,9-dihydro-4*H*-indeno[1,7-*fg*]indole (V; R = indan-5-yl)	197	$C_{23}H_{19}N$	89·3	6·3	4·4	89·3	6·2	4·5
Picrate	185	$C_{29}H_{22}N_4O_7$	64·4	4·3	10·4	64·7	4·1	10·4
8-(*p*-Methoxyphenyl)-5,9-dihydro-4*H*-indeno[1,7-*fg*]indole (V; R = *p*-MeO·C$_6$H$_4$)	260	$C_{21}H_{17}NO$	83·9	5·8	4·5	84·2	5·7	4·7
8-Phenyl-9*H*-phenaleno[1,9-*fg*]indole (VI; R = Ph)	285	$C_{24}H_{15}N$	91·2	4·7	4·2	91·4	4·5	4·4
8-(*p*-Chlorophenyl)-9*H*-phenaleno[1,9-*fg*]indole (VI; R = *p*-ClC$_6$H$_4$)	250 (decomp.)	$C_{24}H_{14}ClN$	82·2	4·0	3·8	82·4	4·0	4·0

[a] Recrystallised from cyclohexane, benzene, or ethanol–benzene, as colourless leaflets or prisms. Picrates or dipicrates crystallised from ethanol or ethanol–benzene as brown needles.

2-*Phenyl*-1H-*benz*[f]*indole* (III; R = Ph).—Heating 5,6,7,8-tetrahydro-2-phenyl-1*H*-benz[*f*]indole (IV; R = H), followed by sublimation *in vacuo* over 5% palladium–charcoal and recrystallisation from benzene, furnished the indole (III), m.p. 260° (see Table 3).

The new indoles described are currently undergoing tests for carcinogenic and zoxazolamine hydroxylase-inducing activities; results will be reported elsewhere.

We thank the Ligue française contre le Cancer for a Fellowship (to P. B.), and the S.E.I.T.A. for support.

[2/1075 *Received*, 11*th May*, 1972]