784. *The Reaction of Indole with Free Benzyl Radicals*

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The initial products of homolytic benzylation of indole are mainly 1 (=N)-benzylindole and 3-benzylindole. Further attack on 1-benzylindole gives α-(1-indolyl)bibenzyl while further attack on 3-benzylindole gives the 1,3- and 2,3-dibenzylindoles. There is a small amount of benzylation in the benzenoid ring.

Indole is much less reactive towards homolytic substitution than either acridine or phenazine.

THE reactions of pyrene,[1] anthracene,[2] acridine,[3] benzacridines,[4] and phenazine [5] with benzyl radicals have been studied by decomposing t-butyl peroxide in refluxing toluene solutions of these compounds and the present investigation of the reactivity of indole follows the same general plan. Products have been separated by fractional distillation followed by elution chromatography through alumina and identified both spectroscopically and by unequivocal syntheses. As indicated by the work of Cohen, Daly, Kny, and Witkop [6] and of Elvidge and Foster,[7] nuclear magnetic resonance spectroscopy has proved to be particularly helpful for deducing the positions of substituents in the 5-membered ring.

TABLE 1

		Percentage yields	
Product	M. p.	1 Equiv.	3 Equiv.
1-Benzylindole	41·0—42·0°	1·67	2·18
2-Benzylindole	107·0—108·0	2·15	0·00
1,3-Dibenzylindole	70·0—71·0	0·83	0·99
2,3-Dibenzylindole	99·0—101·0	1·11	3·74
?-Benzylindole	77·0—79·0	0·80	0·44

In all reactions much of the indole was not attacked and bibenzyl was formed by dimerisation of benzyl radicals, showing that indole is much less reactive towards homolytic attack than the other heterocyclic compounds mentioned above. The percentage yields of separated pure products from the reactions of indole in toluene with both 1 and 3 equivalents of t-butyl peroxide are given in Table 1; naturally these are minima.

As with electrophilic heterolytic substitution of indole, 2-benzylindole does not appear to be an initial reaction product, but 2,3-dibenzylindole seems to be formed from 3-benzylindole. In a direct experiment it was found that the further substitution of 1-benzylindole

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[1] R. O. C. Norman, G. A. Thompson, and W. A. Waters, *J.*, 1958, 175.
[2] A. L. J. Beckwith and W. A. Waters, *J.*, 1957, 1001.
[3] W. A. Waters and D. H. Watson, *J.*, 1957, 253.
[4] W. A. Waters and D. H. Watson, *J.*, 1959, 2082.
[5] W. A. Waters and D. H. Watson, *J.*, 1959, 2085.
[6] L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Amer. Chem. Soc.*, 1960, **82**, 2184.
[7] J. A. Elvidge and R. G. Foster, *J.*, 1964, 981.

Table 2

N.m.r. spectra: details of observed proton splitting values (τ)

Measurement in carbon tetrachloride at 34°

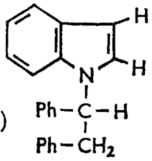
Compound	2-H	3-H	1-Bz	2-Bz	3-Bz	?4-Bz
Indole	3·19, 3·23, 3·28(t)	3·56, 3·59, 3·65(t)	—	—	—	—
1-Benzylindole	3·04, 3·09(d)	3·55, 3·60(d)	4·83(s)	—	—	—
2-Benzylindole	—	3·78, 3·81(d)	—	6·02(s)	—	—
3-Benzylindole	3·29, 3·31(d)	—	—	—	5·94(s)	—
1,3-Dibenzylindole	3·30(s)	—	4·88(s)	—	5·94(s)	—
2,3-Dibenzylindole	—	—	—	6·02(s)	5·90(s)	—
?-Benzylindole	3·06, 3·11, 3·16(t)	3·56, 3·60, 3·65(t)	—	—	—	5·79(s)

Proton shifts due to N–H cannot be observed, for they are masked by the complex aromatic absorptions.

s = singlet; d = doublet; t = triplet

N.m.r. spectrum of α-(1-indolyl)bibenzyl

(I)



3·58, 3·62 (doublet-split by 2-proton)

3·11, 3·18 (doublet-split by 3 proton)

4·27, 4·39, 4·51 (triplet-split by two adjacent protons)

6·41, 6·53 (doublet-split by one adjacent proton)

gave α-(1-indolyl)bibenzyl (I), so that 3-benzylindole may also be the precursor of the 1,3-dibenzylindole.

The unidentified minor product listed in Table 1 has been shown by n.m.r. spectroscopy (Table 2) to have one benzyl group present as a substituent in the benzenoid ring of indole. By an unequivocal synthesis (see Experimental section) it was proved not to be 7-benzylindole, and since the absence of strong infrared absorption in the 800—900 cm.$^{-1}$ region indicated substitution in the 5 or 6 positions to be unlikely we suggest that this minor product may be 4-benzylindole, for which no diagnostic synthesis is reasonably practicable. Substitution at position 4 in indole corresponds to α-substitution in the case of naphthalene; this is the favoured point of homolytic attack.[8]

Since Table 1 indicates that substitution of indole at the nitrogen (position 1) and at carbon atoms are independent concurrent reactions we suggest that the former proceeds *via* an initial hydrogen abstraction from N–H,

$$C_8H_6NH + \cdot R \longrightarrow C_8H_6N\cdot + HR$$
$$C_8H_6N\cdot + \cdot CH_2\cdot Ph \longrightarrow C_8H_6N{-}CH_2\cdot Ph$$

and the latter by benzyl radical addition followed by hydrogen elimination as in the homolytic substitution of benzene, anthracene, or acridine.

Table 3

Positions of infrared absorption (cm.$^{-1}$) in Nujol mulls at 20°

	N–H band	Aromatic C–H bands				
Indole	3400	768	747	722	—	—
1-Benzylindole	—	758	736	717	692	—
2-Benzylindole	3400	790	741	711	695	—
3-Benzylindole	3400	760	743	710	695	—
1-3-Dibenzylindole	—	761	740	730	701	696
2,3-Dibenzylindole	3450	751	742	735	702	—
?4-Benzylindole	3370	769	755	725	701	—
α-(1-Indolylbibenzyl)	—	760	747	736	719	698
7-Benzylindole-2-carboxylic acid ethyl ester	3330	785	767	755	745	708
7-Benzylindole-2-carboxylic acid	3450	781	765	759	748	709
7-Benzylindole	3350	789	762	740	703	—

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[8] P. S. Johnson and W. A. Waters, *J.*, 1962, 4652.

EXPERIMENTAL

Reaction of Indole with Benzyl Radicals.—Indole (11·7 g., 0·1 mol.), t-butyl peroxide (14·6 g., 0·1 mol.), and toluene (600 ml.) were boiled together for 3 days under reflux in an atmosphere of nitrogen. After removal of the solvent at 100°/50 mm. the remainder was distilled in steam to remove bibenzyl (2·5 g.) and unchanged indole (6 g.) (which were easily separated by chromatography through alumina), then taken up in chloroform, dried, and fractionated at 1·4 mm. pressure. The fractions of b. p. up to 180° (3·1 g.), which in part crystallised when cold, were chromatographed through alumina (380 g.) with light petroleum and then benzene as eluents. After separation of small amounts of bibenzyl (0·65 g.) and indole (0·68 g.) there were obtained successively 1-benzylindole (0·35 g.), m. p. 41—42°, 3-benzylindole (0·45 g.), m. p. 107—108°, and a *monobenzylindole* (0·16 g.) which crystallised from light petroleum in fluffy needles, m. p. 77—79° (Found: C, 87·1; H, 6·0; N, 6·2. $C_{15}H_{13}N$ requires C, 86·9; H, 6·3; N, 6·8%). The fraction of b. p. 200—210° (1·6 g.), a brown gum, was chromatographed through alumina (320 g.) and separated into 1,3-*dibenzylindole* (0·25 g.), m. p. 70—71° (Found: C, 88·6; H, 6·5; N, 5·1. $C_{22}H_{19}N$ requires C, 88·8; H, 6·4; N, 4·7%), and 2,3-*dibenzylindole* (0·32 g.), m. p. 99—101° (Found: C, 88·3; H, 6·3; N, 5·0%).

From a similar reaction in which 45 g. (0·3 mol.) of t-butyl peroxide was used the yields of products were 1-benzylindole (0·45 g.), 1,3-dibenzylindole (0·30 g.), 2,3-dibenzylindole (1·11 g.), and the benzylindole of m. p. 77—79° (0·09 g.).

The reaction of 1-benzylindole (0·1 mol.) with t-butyl peroxide (0·1 mol.) in toluene (600 ml.) gave bibenzyl (18·6 g., 59%) and α-(1-*indolyl)bibenzyl*, m. p. 89·0—91·0° (2·52 g., 8·5%) (Found: C, 88·7; H, 6·3; N, 4·9. $C_{22}H_{19}N$ requires C, 88·8; H, 6·4; N, 4·7%), with recovery of 82·7% of unchanged 1-benzylindole.

An independent synthesis of the above compound was attempted without success.

Preparation of Authentic Reference Compounds.—1-Benzylindole was prepared by Plieninger's [9] method of reaction of the sodium derivative of indole with benzyl chloride in liquid ammonia. It crystallised from light petroleum–ether in prims, m. p. 41—42°, yield 67% (Found: C, 86·8; H, 6·2; N, 7·0. Calc. for $C_{15}H_{13}N$: C, 86·9; H, 6·3; N, 6·8%).

3-*Benzyl- and* 2,3-*dibenzyl-indoles.* Indole (10 g.) was added to benzyl alcohol (200 ml.) in which sodium (12 g.) had been dissolved and the mixture was heated for 12 hr. under reflux at 210—240° (cf. Cornforth and Robinson [10]). After removal of the benzyl alcohol at 50 mm. the remainder was distilled in steam until the oil drops which distilled began to crystallise upon cooling. The residue was then extracted into ether, dried, and concentrated to give a purple solid (8·7 g., m. p. 99—106°) which by crystallisation from light petroleum (b. p. 80—100°) followed by chromatography gave 3-benzylindole, m. p. 108—108·5°, which showed typical N–H absorption at 3400 cm.$^{-1}$ (Found: C, 87·0; H, 6·3; N, 6·3%). From the mother-liquors of this crystallisation, by chromatographic separation, there was obtained 2,3-*dibenzylindole* (1·2 g., 5%) which crystallised from light petroleum–ether in pale yellow tablets, m. p. 99—101°. This new compound exhibited N–H absorption at 3400 cm.$^{-1}$ and its n.m.r. spectrum (Table 2) showed the presence of two benzyl groups and the absence of protons in the 2 and 3 positions (Found: C, 88·8; H, 6·3; N, 4·5). When a similar mixture of indole, benzyl alcohol, and sodium was heated at 160—170° for 27 hr. an 87% yield of 3-benzylindole was obtained, not contaminated with 2,3-dibenzylindole. 2-Benzylindole was prepared from 3-benzylindole by the method of Clemo and Seaton [11] and chromatographed in benzene through alumina (yield 30%). It crystallised from light petroleum in needles part of which had m. p. 75·0° and part m. p. 85·0°. Julian and Pikl [12] have reported this dimorphism and the same m. p.s. From aqueous methanol the compound formed needles, m. p. 78·0—85·0°, which showed N–H absorption at 3400 cm.$^{-1}$ and had an n.m.r. spectrum which indicated the presence of one benzyl group and a proton at the 3 position (Found: C, 86·7; H, 6·4; N, 6·7%).

1,3-*Dibenzylindole.* Sodium (0·5 g.) was dissolved in liquid ammonia (20 ml.) containing a trace of ferric nitrate and after 30 min. 3-benzylindole (2·0 g.) and a solution of benzyl chloride (1·1 g.) in dry ether (5 ml.) were added, in turn. Stirring for a further 30 min. was followed by evaporation of the ammonia. The remaining brown solid was dissolved in a mixture of water

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[9] H. Plieninger, *Chem. Ber.*, 1954, **87**, 127.
[10] R. H. Cornforth and R. Robinson, *J.*, 1942, 680.
[11] G. R. Clemo and J. C. Seaton, *J.*, 1954, 2583.
[12] P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.*, 1933, **55**, 2105.

(50 ml.) and ether (50 ml.). The ether layer was separated, dried, and evaporated to leave a brown gum which was chromatographically purified to yield 1,3-dibenzylindole (0·79 g.) which crystallised from light petroleum in colourless needles, m. p. 70·0—71·0°. It had no N–H absorption at 3400 cm.$^{-1}$ and its n.m.r. spectrum (Table 2) confirmed its structure (Found: C, 88·8; H, 6·3; N, 4·7).

7-*Benzylindole*. 2-Aminobenzophenone, prepared both from *o*-benzoylbenzoic acid [13] and from anthranilic acid [14] was reduced [14] to 2-aminodiphenylmethane (m. p. 47—49°). This (6·5 g.) dissolved in acetic (5 ml.) and hydrochloric (13·5 ml.) acids was diazotised at 0° with sodium nitrite (4·5 g.) in water (10 ml.) and the diazo-solution was added dropwise with stirring to a mixture at 0° of ethyl α-methylacetoacetate (5 g.), ethanol (25 ml.), potassium hydroxide (11·5 g.), and water (6·5 ml.). After 20 min. the sticky red precipitate of ethyl pyruvate *o*-benzylphenylhydrazone was collected, washed with cold water, and dried (8·1 g., 78%). The crude hydrazone (4·95 g.) was then added to polyphosphoric acid (4 g.) and heated at 110° for 15 min. After cooling, water (40 ml.) was added and the product was extracted into ether, dried ($MgSO_4$), and after evaporation, chromatographed on alumina using light petroleum–benzene to give *ethyl* 7-*benzylindole*-2-*carboxylate* (0·95 g.) part of which, when further purified by sublimation, had m. p. 131° (Found: C, 77·5; H, 6·0; N, 5·1. $C_{18}H_{17}NO_2$ requires C, 77·4; H, 6·1; N, 5·0%). The ester (0·35 g.) in hot ethanol (2·3 ml.) was hydrolysed by treatment for 6 hr. with caustic potash (30%, 1 ml.), then diluted with water and poured, with stirring, into dilute hydrochloric acid. The precipitated 7-*benzylindole*-2-*carboxylic acid* crystallised from light petroleum–ethanol and after sublimation formed fine needles, m. p. 163·5—165° (Found: C, 76·3; H, 5·1; N, 5·6. $C_{16}H_{13}NO_2$ requires C, 76·5; H, 5·2; N, 5·6%). This acid (0·5 g.) was decarboxylated by heating for 2 hr. at 235° in distilled quinoline (3·6 g.) with a trace of copper oxide (0·04 g.). After cooling to 0° dilute (1 : 2) hydrochloric acid (14 ml.) was added and the product was extracted into ether, dried ($MgSO_4$), the solvent was removed and the residue chromatographed in light petroleum–benzene (1 : 1) to give 7-*benzylindole* which after sublimation had m. p. 67—68·5° and the spectrographic characteristics given in Tables 2 and 3 (Found: C, 86·7; H, 6·5; N, 7·2. $C_{15}H_{13}N$ requires C, 86·9; H, 6·3; N, 6·8%).

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[13] C. L. Hewett, L. J. Lermit, H. T. Openshaw, A. R. Todd, A. H. Williams, and F. N. Woodward, *J.*, 1948, 292.

[14] H. J. Scheifele and D. F. DeTar, *Org. Synth.*, Coll. Vol. IV, p. 34.