The Synthesis of some Alkylbenzocarbazoles

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The preparation is described of five known and eight novel carbazole derivatives, the latter including compounds with alkyl side-chains.

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Carbazoles and benzocarbazoles have recently attracted much attention as proven or potential carcinogens. Dibenzo[*a*,*g*]carbazole also possesses considerable inhibitory powers against the growth of Walker rat carcinoma [1]. Despite considerable synthetic activity in this general area, very few *C*-alkylbenzocarbazoles have previously been described. We now report that such compounds are readily available using the Fischer indole synthesis [2,3,4], followed by dehydrogenation of the resulting hydrocompounds over chloranil [5] or palladised charcoal [3,6].

Compounds prepared are listed in Table 1 which includes four known compounds made by the previously used methods (**3**, **4**, **9**, **10**) and two known compounds previously made by methods other than those presently employed (**12**, **15**). The remaining eight compounds of Table 1 are novel. The method most commonly used for the preparation of dibenzocarbazoles has been the Bucherer reaction, but as stated [1] the relative inaccessibility of substituted naphthylhydrazines renders this method hardly feasible for substituted derivatives.

Conditions used for the Fischer indole syntheses, and details of the products are recorded in Table 2. Of considerable interest are the reactions of α- and β-tetralone with hydrazine: the β-derivative gives directly a high yield of the tetrahydrodibenzocarbazole **11**, but under the same conditions the α-derivative forms only the ketazine and (as shown by the conditions, Table 2) this needs much stronger acid conditions for cyclisation to **14**. A probable reason for this difference is the greater tendency of the β-ketazine to tautomerize into the enamine form (β-tetralone more easily forms an anion than α-tetralone). We could not confirm the reported conversion of ketazine **13** to the dibenzocarbazole **15** by simple thermolysis in 71% yield [7]: in our hands the yield of **15** was around 5%. The acid catalyzed conversion **13** → **14** needed carefully controlled anhydrous conditions (*e.g.* in Table 2 we used anhydrous

Scheme I

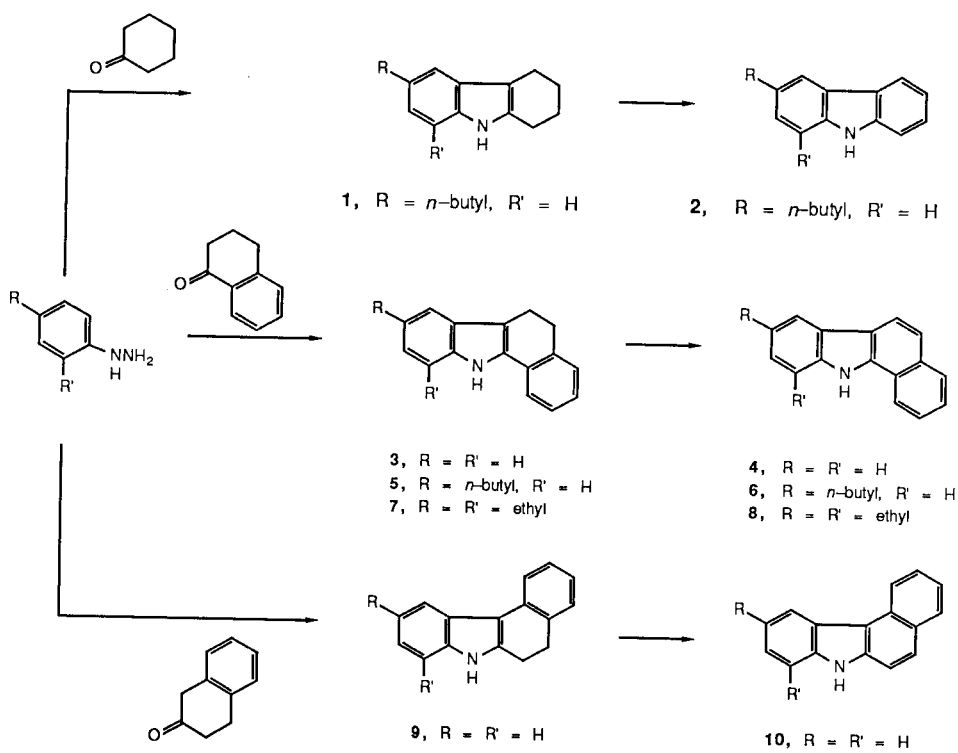

Table 1

Names of Compounds and Infrared Spectra (λ max, cm^{-1})

No.	Name	Phase	Main Infrared Peaks
1	1,2,3,4-tetrahydro-6-*n*-butylcarbazole	(bromoform)	3460 (s), 3400 (s), 2920 (s), 2840 (s), 1590, 1460 (s), 1440 (s), 1375, 1355, 1315, 1280, 1230, 1190, 870, 800, 690
2	6-*n*-butylcarbazole	(bromoform)	3400 (s), 2950, 2920, 2860, 1490, 1460 (s), 1330, 1240, 930, 810 (s), 760, 750, 730, 690
3	5,6-dihydro-11*H*-benzo[*a*]carbazole	(potassium bromide)	3370 (vs), 3020, 2940, 2820, 1500, 1460, 1355, 1300, 1260, 1190, 1090, 1000, 720, 650
4	11*H*-benzo[*a*]carbazole	(potassium bromide)	3440 (vs), 1460, 1445, 1385, 1330, 1305, 1280, 1240, 815 (s), 704 (vs)
5	5,6-dihydro-8-*n*-butyl-11*H*-benzo[*a*]carbazole	(bromoform)	3440 (vs), 2920 (vs), 2860, 1460 (s), 1290 (s), 1260, 755
6	8-*n*-butyl-11*H*-benzo[*a*]carbazole	(bromoform)	3420 (vs), 3040, 2950 (s), 2920 (vs), 2850, 1520, 1455 (vs), 1375, 1300, 1235, 855, 810, 750, 730, 685
7	5,6-dihydro-8,10-diethyl-11*H*-benzo[*a*]carbazole	(neat)	3450 (s), 3050, 3010, 2960 (vs), 2920 (vs), 2860 (s), 1615, 1590, 1500, 1480, 1450 (s), 1420, 1370, 1315, 1290, 1250, 1180, 1060, 855 (s), 800, 760 (vs), 735, 700
8	8,10-diethyl-11*H*-benzo[*a*]carbazole	(bromoform)	3440 (s), 2940 (vs), 2910 (s), 2850, 1520, 1480, 1520, 1480, 1455, 1430, 1375 (s), 1300, 1280, 1270, 1220, 1200, 860 (s), 800 (vs), 730 (s)
9	5,6-dihydro-7*H*-benzo[*c*]carbazole	(potasium bromide)	3360 (vs), 1600, 1540, 1490 (s), 1450 (s), 1420, 1350, 1320, 1270, 1250, 1220, 1180, 1065, 1015, 765 (s), 740 (vs), 695, 680, 645
10	7*H*-benzo[*c*]carbazole	(potassium bromide)	3360 (s), 3020, 1580, 1520, 1440, 1340, 1320, 1265, 1240, 1200, 930, 790 (s), 730 (s), 665
11	5,6,8,9-tetrahydro-7*H*-dibenzo[*c,g*]carbazole	(bromoform)	3430 (vs), 2920, 2880, 2820, 1595, 1510, 1475, 1455, 1415, 1355, 750 (vs)
12	7*H*-dibenzo[*c,g*]carbazole	(bromoform)	3400 (s), 1370, 1310, 1010, 795 (vs), 765, 740 (s)
14	5,6,7,8-tetrahydro-13*H*-dibenzo[*a,i*]carbazole	(bromoform)	3450 (s), 2930, 2890, 2840, 1610 (s), 1500 (vs), 1445, 1290 (vs), 1265, 800, 760 (vs), 740
15	13*H*-dibenzo[*a,i*]carbazole	(bromoform)	3430 (s), 1380, 1290, 1190, 800 (vs), 770, 730 (s)

Scheme 2

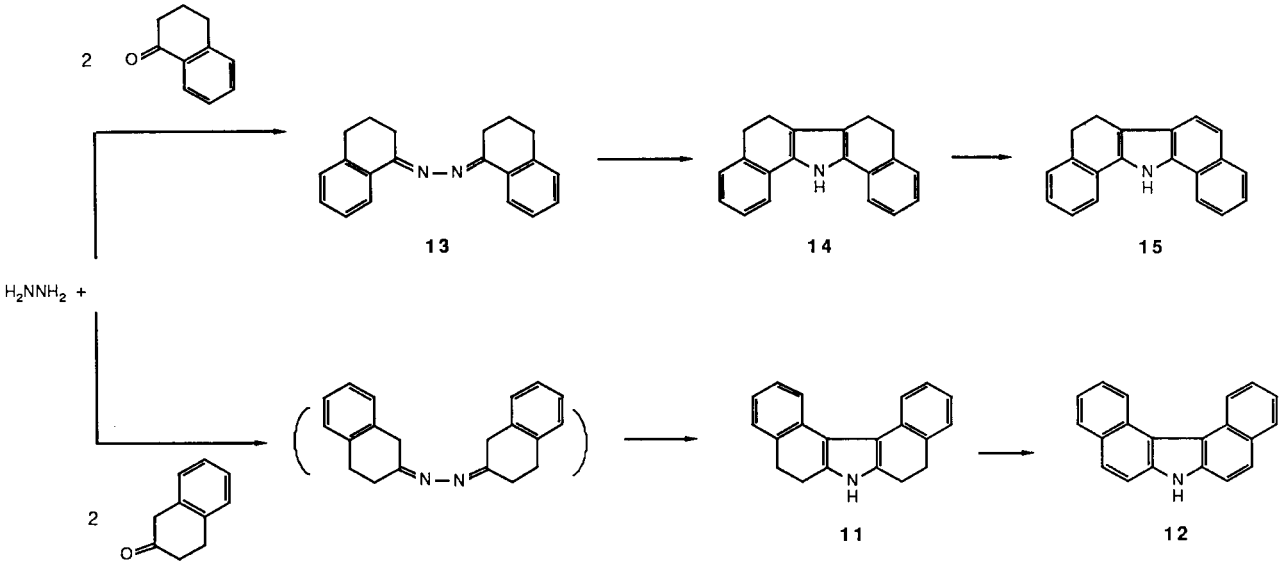

Table 2

Conditions of the Fischer Indole Syntheses

	Hydrazine $RNHNH_2$		Ketone		Solvent		Heating		Recrystallization		Yield	
Preparation of	R	amount (g)	nature	amount (g)	nature	amount (ml)	time (h)	temp (°C)	Solvent	mp [a] (°C)	Wt (g)	%
1	p-(n-Bu)C_6H_4	24.0	cyclohexanone	11.8	AcOH	41.0	12.0	120	CH_3OH	95-97 [b]	18.4	67
3	C_6H_5	5.57	α-tetralone	7.46	HCl H_2O	9 25	1.5	100	CH_3OH	164-165 [b]	9.6	86
5	p-(n-Bu)C_6H_4	6.00	α-tetralone	4.37	HCl H_2O	12.6 14.8	4.5	100	CH_3OH	144-145 [d]	6.7	81
7	2,4-$(Et)_2C_6H_4$	7.55	α-tetralone	5.50	HCl H_2O	15.8 150	11.0	100	[e]	liquid [f]	6.5	63
9	C_6H_5	18.5	β-tetralone	25.0	HCl H_2O	29.5 86.0	6.0	100	CH_3OH	102-103 [g]	20.2	54
11	H	1.44	β-tetralone	14.8	AcOH EtOH H_2O	0.1 35.0 1.0	43.0	78	C_6H_6	249-250 [h]	10.0	82
14	[i]	5.12	—	—	AcOH dry HCl	20.0	41.5	120	C_6H_6 [j]	164-166 [k]	2.1	44

[a] All crystallized as prisms except **7**. [b] *Anal.* Calcd. for $C_{16}H_{21}H$: C, 84.58; H, 9.25; N, 6.17; ms: m/e 227.1674. Found: C, 84.27; H, 9.35; N, 6.15; ms: m/e 227.1674. [c] Lit [3] mp 163-164°. [d] *Anal.* Calcd. for $C_{20}H_{21}N$: C, 87.23; H, 7.69; N, 5.08. Found: C, 87.29; H, 8.01; N, 5.00. [e] Extracted with ethyl acetate, and purified by chromatography on silica gel with a methylene chloride and hexane mixture (2/10, v/v). [f] *Anal.* Calcd. for $C_{20}H_{21}N$: C, 87.23; H, 7.69; N, 5.08. ms: m/e 275.1674. Found: C, 86.97; H, 7.75; N, 4.90; ms: m/e 275.1659. [g] Lit [3] mp 102-103°. [h] *Anal.* Calcd. for $C_{20}H_{17}N$: C, 88.56; H, 6.27; N, 5.17. Found: C, 88.27; H, 6.52; N, 5.00. [i] α-Tetralone ketazine used as a starting material. See references [7,13]. [j] Before recrystallization, the reaction mixture was extracted with ether and then purified by chromatography on silica gel with benzene and hexane mixture (9/1, v/v). [k] *Anal.* Calcd. for $C_{20}H_{17}N$: C, 88.56; H, 6.27; N, 5.17; ms: m/e 271.1361. Found: C, 88.23; H, 6.50; N, 5.11; ms: m/e 271.1357.

Table 3

Dehydrogenation of Di- and Tetrahydrocarbazoles

Preparation of	Wt(g) starting material	Wt(g) Pd/C (5%)	Heating [a] time (minutes)	C_6H_6 extraction (ml)	mp (°C)	Products crystal form	Yield (g)	%	Literature mp (°C)	Literature reference
2	8.95	3.47	40	225	131-133	needles	7.74 [b]	88	—	—
4	4.50	0.9	20	90	227-229	prisms	3.50	78	227-229	[3]
6	2.00	0.32	30	50	194-196	prisms	1.32 [c]	66	—	—
8	2.12	0.37	30	50	116-118	prisms	1.60 [d]	76	—	—
10	8.80	1.76	30	150	135-136	microcrystals	5.10	58	135-136	[3]
12	2.00	0.65	30	20	152-154	prisms	1.54 [e]	78	154	[1]
15	4.74	1.50	30	60	222-224	prisms	2.70 [f]	58	223.5-224	[12]

[a] All heated at 250-260°C. [b] *Anal.* Calcd. for $C_{16}H_{17}N$: C, 86.10; H, 7.62; N, 6.28; ms: m/e 223.1361. Found: C, 85.82; H, 7.70; N, 6.20; ms: m/e 223.364. [c] *Anal.* Calcd. for $C_{20}H_{19}N$: C, 87.91; H, 6.96; N, 5.12. Found: C, 87.82; H, 7.24; N, 4.96. [d] *Anal.* Calcd. for $C_{20}H_{19}N$: C, 87.91; H, 6.96; N, 5.12. Found: C, 88.20; H, 7.24; N, 4.98. [e] *Anal.* Calcd. for $C_{20}H_{13}N$: C, 89.89; H, 4.87;N, 5.24. Found: C, 89.60; H, 4.98; N, 5.08. [f] *Anal.* Calcd. for $C_{20}H_{13}N$: C, 89.89; H, 4.87; N, 5.24. Found: C, 89.89; H, 4.85; N, 5.15.

hydrogen chloride in acetic acid), otherwise hydrolysis back to α-tetralone occurred.

Conditions for the dehydrogenation of the di- and tetrahydrocarbazoles and the characterization of the products are given in Table 3. The transformations proceeded smoothly and in good yield to give well crystallised products.

Proton NMR Spectra.

Table 4 records some of the characteristic ^1H nmr bonds. The carbazole NH peak is found at *ca* 11-12 ppm for DMSO solution, but at *ca* 8 ppm for deuteriochloroform solution [8]. The benzene ring CH signals (not shown) form a multiplet at 9-7 ppm which is not diagnostically very helpful, but the aliphatic CH_2 and CH_3 signals are

Table 4

Proton NMR Spectral Shifts

Compound [a]	NH (s)	CH_2 alpha to ring				Other CH_2			CH_3			
	δ	δ	m	J(Hz)	H	δ	m	H	δ	m	J(Hz)	H
1	10.51	2.69	m		6	2.13-1.10	m	8	0.93	t	5	3
2	11.13	2.76	t	8	2	2.00-1.10	m	4	0.93	t	6	3
3	11.60	3.00	s		4							
5	11.17	2.90-2.53	m		6	1.93-1.10	m	4	0.90	t	5	3
6	11.91	2.80-2.54	t	6	2	1.90-1.13	m	4	0.84	t	6	3
7	7.53	2.79	s		4				1.26	t	8	6
		2.66	q	8	4							
8	8.20	2.93	q	8	2				1.41	t	8	3
		2.81	q	8	2				1.36	t	8	3
9	11.52	3.07	s		4							
11	10.86	2.92-2.50	m		8							
14	11.02	2.87	t	8	4							
		2.61	t	8	4							

[a] All spectra were run in DMSO-d_6 except **7** and **8** which were run in deuteriochloroform.

clearly identifiable and serve to characterize both the degree of hydrogenation of the ring system and the nature of the attached alkyl group(s).

The ^{13}C-nmr spectra afforded further evidence for the structures. These spectra will be reported elsewhere as part of a larger investigation [14].

EXPERIMENTAL

All melting points are uncorrected and were taken on a Bristoline Hot-Stage apparatus. The ir spectra were obtained on a Perkin-Elmer 283B infrared spectrophotometer. The ^{1}H-nmr spectra were obtained at 60 MHz on a Varian EM 360L nmr spectrometer, with TMS as internal standard. The ^{13}C-nmr spectra were obtained at 25 MHz on a JEOL FX-100 nmr spectrometer, referenced to solvent (δ DMSO-d_6 = 39.5). Low and high resolution mass spectra were obtained on an AEI ms 30 mass spectrometer. Microanalyses were performed in house, on a Carlo Erba 1106 elemental analyzer.

Materials.

Phenylhydrazine, anhydrous hydrazine, α-tetralone, β-tetralone and cyclohexanone were obtained from Aldrich Chemical Company, Inc. and were used without further purification. Silica gel was MCN Silica gel 60 (230-400 mesh).

p-Butylphenylhydrazine hydrochloride (mp 232-234°, lit [9] mp 232-234°), 2,4-diethyl-1-nitrobenzene (bp 133°/4 mm, lit [10] bp 133°/4 mm), 2,4-diethyl-1-aminobenzene (bp 141°/30 mm, lit [11] bp 141°/30 mm), and α-tetralone ketazine (**13**) (mp 143-144°, lit [13] mp 143-144°) were prepared by the literature methods indicated.

2,4-Diethylphenylhydrazine Hydrochloride.

Sodium nitrite (7.68 g, 0.111 mole) in water (32 ml) was added during 30 minute to a stirred, cold (0°) suspension of 2,4-diethyl-1-aminobenzene (16 g, 0.107 mole) in 6*N* hydrochloric acid (128 ml). After an additional 15 minutes stannous chloride.$2H_2O$ (71.2 g, 0.315 mole) in 6*N* hydrochloric acid (128 ml) was added slowly, and the resulting suspension was stirred for 4 hours at 0°. The solid was filtered off and dissolved in 40% aqueous potassium hydroxide (160 ml) covered with ethyl acetate (160 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 160 ml). The combined organic extracts were washed with 10% hydrochloric acid (80 ml) and the solvent removed. The residue was recrystallized from benzene (200 ml) and ethanol (17 ml) to give white plates (16 g, 75%). mp 181-182°; ^{1}H-nmr (DMSO-d_6): δ 1.15 (6H, t, J = 7 Hz, $2CH_3$), 2.73-2.33 (4H, m, $2CH_2$), 3.33 (H_2O), 6.64 (3H, s, 3Ar-*H*), 7.33 (1H, quartet, N*H*), 9.82 (3H, d, J = 2 Hz, NH_3^+).

1,2,3,4-Tetrahydro-6-*n*-butylcarbazole (**1**).

Cyclohexanone (11.75 g, 0.12 mole), glacial acetic acid (43 g) and *P*-*n*-butyl(phenylhydrazine hydrochloride (24 g, 0.12 mole) were refluxed for 12 hours. The mixture was then cooled to 5°. The solid was filtered off, washed with water (12 ml), with 75% ethanol (12 ml), and recrystallized from ethanol (145 ml) (carbon) to give carbazole **1**.

5,6-Dihydro-8,10-diethyl-11*H*-benzo[*a*]carbazole (**7**).

6*N*-Hydrochloric acid (15.8 ml, 0.038 mole), water (150 ml) and 2,4-diethylphenylhydrazine hydrochloride (7.55 g, 0.0377 mole) were stirred under reflux. α-Tetralone (5.50 g, 0.0377 mole) was added dropwise during 5 minutes and the mixture stirred under reflux for an additional 11 hours, then cooled to 20° and extracted with ethyl acetate (3 × 150 ml). The combined extracts were washed with water (2 × 125 ml) and dried (magnesium sulfate). Removal of the solvent and purification of a portion of the residue (3.5 of 9.50 g) through a column of silica gel (200 g) with methylene chloride:hexane (2:10, v/v) as eluent gave a yellow oil (2.4 g) (one spot on tlc), which slowly solidified (mp 193-195°).

6-*n*-Butylcarbazole (**2**).

1,2,3,4-Tetrahydro-6-*n*-butylcarbazole (8.95 g) and 5% palladium charcoal (3.47 g) were heated at 250 ~ 260° for 40 minutes. The mixture was then extracted with benzene (225 ml) and the extract concentrated to 80 ml to yield the compound **2** (7.74 g, 88%).

Other dehydrogenations of hydrogenated carbazoles were carried out similarly the results are recorded in Table 3.

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