Preparation of a Series of 3- and 6-Substituted 1,2,3,4-Tetra- and 1,2,3,4,4a,9a-Hexa-hydrocarbazoles

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A number of 3- and 6-substituted *N*-methyl-1,2,3,4,4a,9a-hexahydrocarbazoles, geometry *syn cis* and *cis* respectively, have been prepared and characterised; the system has been designed as suitable for use in an examination of the transmission of substituent effects. The hexahydrocarbazoles are generally prepared by hydrogenation in strongly acidic solution of the corresponding 1,2,3,4-tetrahydrocarbazoles. The substituents are: 3-CO_2H, CH_2OH, CH_2OMe, CH_2OTs, CH_2CN, and CH_2Cl; and 6-CO_2Et, CH_2OH, CH_2OMe, CH_2CN, and CMe_2CN.

THERE has been, for many years, much interest in the detailed mechanism of the transmission of substituent effects in both saturated and unsaturated molecules. In particular the relative importance of long-range electrostatic effects (field effects) and bond polarisations (inductive effects) has been difficult to establish.[1] Part of the difficulty is in the choice of model compounds which: (*a*) may be substituted at defined distances from the reaction centre; (*b*) are conformationally rigid; and (*c*) participate in reactions or equilibria which are sufficiently sensitive to polar substituent effects to allow a meaningful analysis in terms of rival hypotheses concerning the transmission of polar effects. Model compounds which have been so used include: 4-substituted bicyclo[2.2.2]octanecarboxylic acids;[1b] substituted naphthoic acids;[1c] substituted phenylacetic acids;[1d] and *trans*-4-substituted cyclohexanecarboxylic acids.[1e] Experiments using these compounds and aimed at distinguishing between the effectiveness of transmission of polar effects across saturated and aromatic systems must involve separate studies of at least two series of compounds. The interpretation of results may, therefore, be complicated, for a chosen reaction, by differences not only in the transmission of polar effects but in solvation or steric hindrance at the reaction centre(s).

In this context we describe the preparation, *via* tetrahydrocarbazoles, of a number of *N*-methyl-*cis*-1,2,3,4,4a,9a-hexahydrocarbazoles substituted with groups of the type CH_2X in the 3- or 6-positions. The geometry of the 3-substituted hexahydrocarbazole system has previously been discussed [2] and the basicity and reactivity of such compounds has been shown to be sensitive to polar effects.[3] The great advantage of this model system is that the environment of the reaction centre (the nitrogen atom) is the same for reactions susceptible to polar effects across a saturated system (from the 3-position) and across an aromatic system (from the 6-position). The disadvantage is that preparative difficulties have precluded the study of a large range of substituents. The use of these compounds in a study of modes of transmission of substituent effects will be discussed elsewhere.

RESULTS AND DISCUSSION

N-Methyltetrahydrocarbazoles were prepared by the routes summarised in Scheme 1. For the initial step, using the Fischer indole synthesis, strongly acidic conditions were required to effect condensation. Even so the yield of *N*-methyltetrahydrocarbazole-3-carboxylic acid was surprisingly low (30%). The yield of

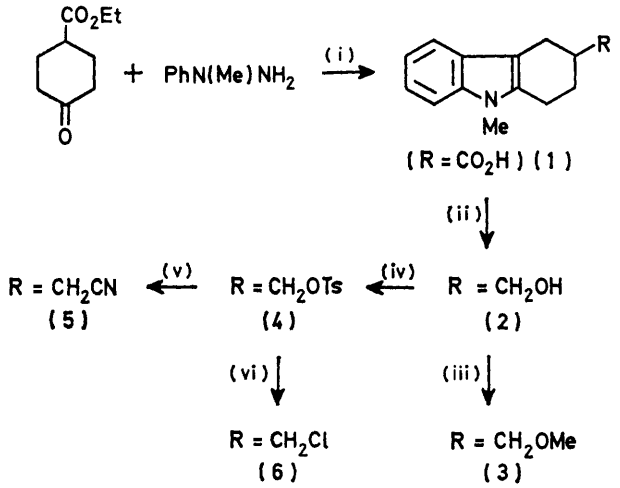
[1] (*a*) N. B. Chapman, J. Shooter, and J. H. P. Utley, *J. Chem. Soc.*, 1962, 1824; (*b*) J. D. Roberts and W. T. Moreland, *J. Amer. Chem. Soc.*, 1953, **75**, 2167; (*c*) M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3539; (*d*) K. Bowden, *Canad. J. Chem.*, 1963, **41**, 2781; (*e*) S. Seigel and J. M. Komarmy, *J. Amer. Chem. Soc.*, 1959, **82**, 2547; (*f*) R. Daniell, A. Ricca, and J. H. Todd, *J.C.S. Perkin II*, 1972, 1547, 2107.

[2] (*a*) A. Smith and J. H. P. Utley, *J. Chem. Soc.* (*C*), 1970, 1; (*b*) D. Shaw, A. Smith, and J. H. P. Utley, *J. Chem. Soc.* (*B*), 1970, 1161.

[3] A. Smith and J. H. P. Utley, *J. Chem. Soc.* (*B*), 1971, 1201.

tetrahydrocarbazole was no higher for condensation between phenylhydrazine and 4-ethoxycarbonylcyclohexanone; yields of 70—80% are normal for this reaction.[2a]

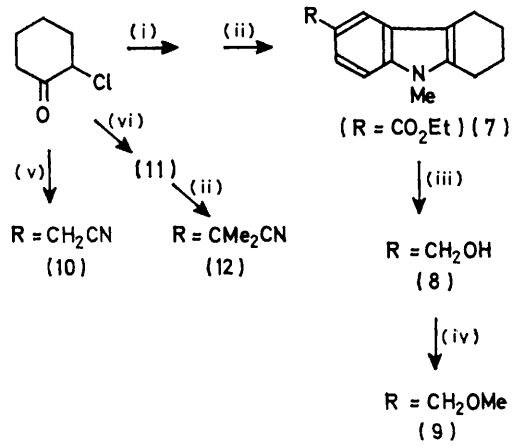
The 6-substituted tetrahydrocarbazoles were prepared according to Scheme 2; the key initial step was the



SCHEME 1 *Reagents:* (i), AcOH–HCl; (ii) $LiAlH_4$; (iii) NaH–MeI–DMF; (iv) *p*-Me·C_6H_4·SO_2Cl–pyridine; (v) NaCN–DMF; (vi) C_5H_5N·HCl–DMF

Bischler condensation [4] of 2-chlorocyclohexanone with the appropriately substituted aniline.

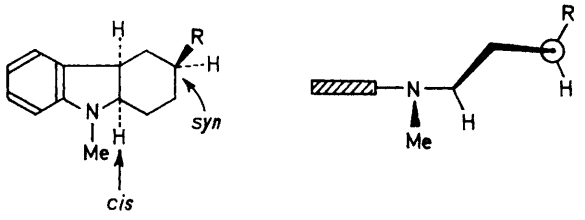
Several difficulties were encountered in trying to introduce at the 6-position the range of $-CH_2Y$ type substituents which were introduced at the 3-position. Attempts to prepare the tosylate of the 6-hydroxymethyl compound failed. Not surprisingly 6-hydroxymethyltetrahydrocarbazole behaves as a benzylic alcohol and



SCHEME 2 *Reagents:* (i) *p*-H_2N·C_6H_4·CO_2Et; (ii) Na–NH_3–MeI; (iii) $LiAlH_4$; (iv) NaH–MeI–DMF; (v) *p*-H(Me)N·C_6H_4·CH_2CN; (vi) *p*-H_2N·C_6H_4·CH_2CN

benzyl tosylates are very reactive. For example, *p*-methoxybenzyl tosylate decomposes rapidly [5] even at −60 °C. The 6-cyanomethyl derivative was, therefore, prepared by direct condensation of 2-chlorocyclohexanone with *p*-methylaminobenzyl cyanide. Condensation involving *p*-aminobenzyl cyanide gave the corresponding tetrahydrocarbazole but, because of the acidity of the benzylic hydrogen atoms, subsequent methylation could not be restricted to the nitrogen atom. Treatment of 6-cyanomethyl-1,2,3,4-tetrahydrocarbazole with methyl iodide in sodamide–liquid ammonia resulted in the formation in good yield (70%) of the trimethylated compound (12).

N-*Methylhexahydrocarbazoles: Preparation and Stereochemistry.*—Reduction of the C(4a)–C(9a) double bond of both 3- and 6-substituted tetrahydrocarbazoles was achieved by catalytic hydrogenation in ethanol–fluoroboric acid solution at room temperature and at atmospheric pressure.[2a,6] For the 3-cyanomethyl compound it was necessary to ascertain the relative rates of reduction of the carbon–carbon double bond and the nitrile group. The rate of hydrogen uptake by equivalent amounts of acetonitrile and tetrahydrocarbazole were compared under comparable conditions. Hydrogen uptake by the tetrahydrocarbazole was about twice as fast as for acetonitrile. Consequently controlled hydrogenation of 3-cyanomethyltetrahydrocarbazole in dioxan–fluoroboric acid solution was successful.



Configuration of *cis,syn*-3-substituted hexahydrocarbazoles

The 6-hydroxymethyl- and 6-methoxymethyl-hexahydrocarbazoles were not accessible by hydrogenation of the corresponding tetrahydrocarbazoles. For these compounds hydrogenolysis of the benzylic substituent was significantly faster than hydrogenation of the C(4a)–C(9a) double bond. The required compounds were subsequently obtained from 6-ethoxycarbonyl *N*-methylhexahydrocarbazole using the reactions deployed for the 3-substituted compounds (Scheme 1).

G.l.c. analysis of the hydrogenated products revealed the presence of stereoisomers of the hexahydrocarbazoles. For the 6-substituted compounds two isomers were obtained, generally in the ratio of *ca.* 97% : 3%. The major isomer is the product of *cis*-hydrogenation [2a,6] and, being the more volatile isomer, is conveniently isolated by fractional distillation. For the 3-substituted compounds g.l.c. analysis gave three components in the proportions 85 : 13 : 2; these proportions did not vary significantly with the 3-substituent. The major isomer in each case was isolated by preparative scale g.l.c. and *cis,syn* stereochemistry assigned (Figure). The evidence

[4] E. Campaigne and R. D. Lake, *J. Org. Chem.*, 1959, **24**, 478.
[5] J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, 1953, **75**, 3443.
[6] A. Smith and J. H. P. Utley, *Chem. Comm.*, 1965, 427.

for the major isomers in this series having *cis,syn* stereochemistry has been presented [2b] in detail. Essentially the assignment followed from a comparison of ^{1}H n.m.r. spectra of the *NN*-dimethyl quaternary iodides for isomers of the 3-substituted hexahydrocarbazoles with the spectrum of the corresponding derivative of the only isomer produced by hydrogenation, in acidic solution, of 3-t-butyl-1,2,3,4-tetrahydrocarbazole. For compelling conformational reasons only the *cis,syn*-3-t-butylhexahydrocarbazole is produced. Detailed assignment and analysis of the n.m.r. spectra [2] allied to double-irradiation experiments [2b] confirmed the conclusion about configuration and also demonstrated that the *cis,syn*-isomers existed in a rigid, probably flattened boat conformation (Figure).

The minor isomers (13 and 2%) are probably the *cis-anti*- and a *trans*-isomer. The total *cis* : *trans* ratio is, therefore, *ca.* 98 : 2 which corresponds to the ratio found for hydrogenation of the parent, unsubstituted, *N*-methyltetrahydrocarbazole.

EXPERIMENTAL

3-Substituted-*N*-methyl-1,2,3,4-tetrahydrocarbazoles. Literature methods were used to prepare 4-ethoxycarbonylcyclohexanone [7] and *N*-methyl-*N*-phenylhydrazine.[8]

N-*Methyl*-1,2,3,4-*tetrahydrocarbazole*-3-*carboxylic Acid* (1).—4-Ethoxycarbonylcyclohexanone (10 g, 0.06 mol) in glacial acetic acid (50 cm^3) was heated under reflux, with stirring, for *ca.* 10 min. *N*-Methylphenylhydrazine (15 g, 0.12 mol) was added during 30 min. Concentrated hydrochloric acid was added after a further 30 min until the reaction mixture changed from orange to a dark red colour. After being boiled for a further hour, the reaction mixture was poured into water (1.5 l). A fine powdery solid separated after several hours and this was filtered off, washed with water, and crystallised from benzene; yield, 30%; m.p. 175—176 °C (lit.,[9] m.p. 174—177 °C); $\nu_{max.}$(Nujol) 1 705 (C=O stretch) and 735 cm^{-1} (1,2-disubstitution); δ_H($CDCl_3$) 10 16 (1 H, CO_2H), 7.5—7.0 (4 H, m, Ar), 3.56 (3 H, s, N–CH_3), and 3.2—2.0 (7 H, m, alicyclic) (Found: C, 73.75; H, 6.65; N, 5.9. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11%).

3-*Hydroxymethyl*-N-*methyl*-1,2,3,4-*tetrahydrocarbazole* (2).—This compound was prepared by addition of *N*-methyl-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid (4 g, 0.017 mol) to a suspension of an excess of lithium aluminium hydride in ether. The product was crystallised from ethanol; yield, 80%; m.p. 102—103 °C; $\nu_{max.}$(Nujol) 3 300 (OH) and 730 cm^{-1} (1,2-disubstitution); δ_H($CDCl_3$) 7.90—7.41 (4 H, m, Ar), 3.85 (2 H, d, J = 6 Hz, CH_2), 3.77 (3 H, s, N–CH_3), 3.05—2.50 (7 H, m, alicyclic), and 1.72 (1 H, s, disappears in D_2O, OH) (Found: C, 78.45; H, 8.15; N, 6.15. $C_{14}H_{17}NO$ requires C, 78.10; H, 7.96; N, 6.51%).

3-*Tosyloxymethyl*-N-*methyl*-1,2,3,4-*tetrahydrocarbazole* (4).—This compound was prepared by treatment of the corresponding alcohol (3.5 g, 0.016 mol) with tosyl chloride (7.5 g, 0.039 mol) in dry pyridine (50 cm^3). The product was crystallised from light petroleum (b.p. 40—60 °C); yield 75%, m.p. 90—91 °C; $\nu_{max.}$(Nujol) 1 360s and 1 180d (S=O stretch) and 735 cm^{-1} (1,2-disubstitution); δ_H($CDCl_3$) 7.89—7.11 (8 H, m, Ar), 4.10 (2 H, d, J = 6 Hz, CH_2), 3.59 (3 H, s, N–CH_3), and 2.45 (3 H, s, $PhCH_3$) (Found: C, 68.2; H, 6.35; N; 3.5. $C_{24}H_{23}NO_3S$ requires C, 68.35; H, 6.23; N, 3.7%).

3-*Cyanomethyl*-N-*methyl*-1,2,3,4-*tetrahydrocarbazole* (5).—Sodium cyanide (1.6 g, 0.033 mol), partially dissolved in dry dimethylformamide (20 cm^3), was added to a solution of 3-tosyloxymethyl-*N*-methyltetrahydrocarbazole (4 g, 0.011 mol) in dimethylformamide (25 cm^3) and the mixture was heated at *ca.* 50 °C for 12 h. Conventional work-up and crystallisation from light petroleum (40—60 °C) gave the product; yield, 80%, m.p. 118—120 °C; M^+, *m/e* 224.1309 ($C_{15}H_{16}N_2$ requires 224.1313) (Found: C, 80.25; H, 7.25; N, 12.15. $C_{15}H_{16}N_2$ requires C, 80.32; H, 7.19; N, 12.49%); $\nu_{max.}$(Nujol) 2 240 (C≡N stretch) and 730 cm^{-1} (1,2-disubstitution); δ_H($CDCl_3$) 7.50—7.01 (4 H, m, Ar), 3.59 (3 H, s, N–CH_3), and 2.42 (2 H, d, CH_2CN).

3-*Methoxymethyl*-N-*methyl*-1,2,3,4-*tetrahydrocarbazole* (3).—Sodium hydride (0.25 g, 50% dispersion in oil) was added during 10 min to a solution of 3-hydroxymethyl-*N*-methyltetrahydrocarbazole (1 g, 0.0047 mol) in a mixture of freshly distilled dimethylformamide (35 cm^3) and dry 1,2-dimethoxyethane (15 cm^3) kept at *ca.* −15 °C. Additional sodium hydride suspension (0.25 g) was then added to the mixture the temperature of which was allowed to rise to *ca.* 15 °C. On cooling, methyl iodide (1 g, 0.007 mol) was added to the reaction mixture which was then stirred for 1 h. Work-up and crystallisation from methanol gave the product; yield 60%, m.p. 80—81 °C; M^+, *m/e* 229.1461 (Calc. for $C_{15}H_{19}NO$: 229.1467) (Found: C, 79.2; H, 8.35; N, 6.1. $C_{15}H_{19}NO$ requires C, 78.56; H, 8.35; N, 6.11%); $\nu_{max.}$(Nujol) 1 135 (C–O stretch, acyclic ether) and 730 cm^{-1} (1,2-disubstitution); δ($CDCl_3$) 3.41 (3 H, s, N–CH_3), 3.58 (3 H, s, OCH_3), and 7.49—7.01 (4 H, m, Ar).

3-*Chloromethyl*-N-*methyl*-1,2,3,4-*tetrahydrocarbazole* (6).—3-Tosyloxymethyl-*N*-methyltetrahydrocarbazole (1 g, 0.0027 mol) was dissolved in freshly distilled dimethylformamide (20 cm^3) and pyridinium chloride (1 g, 0.0087 mol) was added to it and the mixture heated overnight at 80 °C. Work-up and crystallisation from aqueous acetone gave the product; yield, 70%, m.p. 72—73 °C; $\nu_{max.}$(Nujol) 1 615 and 1 585 (weak, C=C) and 740 cm^{-1} (1,2-disubstitution); M^+, *m/e* 233.0968 (Calc. for $C_{14}H_{16}ClN$: 233.0971); δ_H($CDCl_3$) 7.55—7.01 (4 H, m, Ar), 3.60 (2 H, d, $-CH_2Cl$), and 3.62 (3 H, s, N–CH_3).

6-*Substituted* N-*Methyl*-1,2,3,4-*tetrahydrocarbazoles*.—Of the starting materials required for the Bischler condensation, *p*-aminobenzyl cyanide was prepared by electrochemical reduction of *p*-nitrobenzyl cyanide; [10] in our hands reported procedures involving selective catalytic hydrogenation failed. *N*-Methyl-*p*-aminobenzyl cyanide was prepared by methylation of *p*-aminobenzyl cyanide using trimethyl orthoformate in sulphuric acid.[11]

Ethyl 1,2,3,4-*Tetrahydrocarbazole*-6-*carboxylate*.—2-Chlorocyclohexanone (10 g, 0.076 mol) was gradually added, at 140 °C, to an excess of ethyl *p*-aminobenzoate (20 g, 0.12 mol). The temperature of the reaction mixture was raised to 160 °C and allowed to cool after 15 min. The reaction mixture was boiled with dilute hydrochloric acid and the product was extracted with boiling ether. Work-up was followed by crystallisation from methanol; yield

[7] R. H. Martin and R. Robinson, *J. Chem. Soc.*, 1943, 497.
[8] W. W. Hartman and L. J. Roll, *Org. Synth.*, Coll. Vol. II, 460, 418.
[9] L. M. Rice and K. R. Scott, *J. Medicin. Chem.*, 1970, **13**, 308.
[10] P. E. Iversen, J. H. P. Utley, and S. O. Yeboah, *Org. Prep. and Proc. Int.*, 1973, **5**, 129.
[11] R. M. Roberts and P. J. Vogt, *Org. Synth.*, Coll. Vol. IV, 420.

35%, m.p. 116—118 °C; M^+, *m/e* 257 ($C_{16}H_{19}NO_2$); $\nu_{max.}$(Nujol) 3 315 (NH), 1 690 (benzoate C=O stretch), 1 625 and 1 590 (C=C), and 770 cm^{-1} (1,2,4-trisubstitution); $\delta_H(CDCl_3)$ 8.11—7.02 (3 H, m, Ar), 4.52 (2 H, q, J = 7 Hz, CH_2), 1.41 (3 H, t, J = 7 Hz, CH_3), and 2.69 and 1.91 (4 H each, m, cyclic CH_2).

Ethyl N-Methyl-1,2,3,4-tetrahydrocarbazole-6-carboxylate (7).—*N*-Methylation of ethyl tetrahydrocarbazole-6-carboxylate was effected by treating the sodium salt with methyl iodide in liquid ammonia; yield 80%, m.p. 105—106 °C; $\nu_{max.}$(Nujol) 1 694 (benzoate C=O stretch), 1 615 (C=C), 1 230—1 260 (d, benzoate C–O stretch), and 770 cm^{-1} (1,2,4-trisubstitution); $\delta_H(CDCl_3)$ 8.19—7.11 (3 H, m, Ar), 4.39 (2 H, q, J = 7 Hz, CH_2), 1.39 (3 H, t, J = 7 Hz, CH_3), 3.58 (3 H, s, N–CH_3), and 2.69 and 1.89 (4 H each, m, cyclic CH_2) (Found: C, 74.5; H, 7.3; N, 5.4. $C_{16}H_{19}NO_2$ requires C, 74.68; H, 7.44; N, 5.44%).

6-Hydroxymethyl-N-methyl-1,2,3,4-tetrahydrocarbazole (8).—Ethyl *N*-methyl-1,2,3,4-tetrahydrocarbazole-6-carboxylate (6 g, 0.023 mol) was reduced to the corresponding alcohol using lithium aluminium hydride in dry ether; yield 70%, m.p. 91—92 °C; $\nu_{max.}$(Nujol) 3 300 (OH), 1 000 (C–O stretch), and 800 cm^{-1} (1,2,4-trisubstitution); $\delta_H(CDCl_3)$ 7.49—7.21 (3 H, m, Ar), 4.75 (2 H, s, CH_2), 3.61 (3 H, s, N–CH_3), 1.54 (1 H, s, disappears in D_2O, OH), and 2.72 and 1.89 (4 H each, m, cyclic CH_2) (Found: C, 77.95; H, 7.7; N, 6.5. $C_{14}H_{17}NO$ requires C, 78.10; H, 7.96; N, 6.51%).

6-Methoxymethyl-N-methyl-1,2,3,4-tetrahydrocarbazole (9).—6-Hydroxymethyl-*N*-methyltetrahydrocarbazole (1 g, 0.0047 mol) was converted into the 6-methoxymethyl derivative as described for the 3-methoxymethyl analogue. The product was a pale yellowish liquid which was distilled (short-path) at 155—160 °C at 0.05 mmHg; yield 50%, M^+, *m/e* 229.1466 (Calc. for $C_{15}H_{19}NO$: 229.1467); ν_{max} (film) 1 090 (C–O–C acyclic ether) and 795 cm^{-1} (1,2,4-trisubstitution); $\delta_H(CDCl_3)$ 7.42—7.02 (3 H, m, Ar), 4 52 (2 H, s, CH_2), 3.53 (3 H, s, O–CH_3), 3.33 (3 H, s, N–CH_3), and 2.65 and 1.85 (4 H each, m, cyclic CH_2)

Attempted Preparation of 6-Tosyloxymethyl-1,2,3,4-tetrahydrocarbazole.— 6-Hydroxymethyl-*N*-methyltetrahydrocarbazole (2 g, 0.0093 mol) in dry pyridine (25 cm^3) was treated with toluene-*p*-sulphonyl chloride (4 g) as described for the 3-methyltosylate analogue. A reddish amorphous material separated when the reaction mixture was poured onto ice. Attempts to obtain crystals from this material proved unsuccessful.

Attempted Preparation of 6-Chloromethyl-N-methyl-1,2,3,4-tetrahydrocarbazole.—Thionyl chloride (1 g) was added during 1 h to a solution of 6-hydroxymethyl-*N*-methyltetrahydrocarbazole (1 g) in dry pyridine (1 cm^3). The reaction mixture was heated at 90 °C for 1 h to give a tar which was insoluble in ether.

6-Cyanomethyl-1,2,3,4-tetrahydrocarbazole (11).—2-Chlorocyclohexanone was condensed with *p*-aminobenzyl cyanide by the Bischler reaction as described for the preparation of 6-ethoxycarbonyltetrahydrocarbazole.

The ether extract was purified by column chromatography (Al_2O_3, 10% ether–light petroleum); yield 10%, m.p. 87—88 °C; M^+, *m/e* 210.1568 (Calc. for $C_{14}H_{14}N_2$: 210.1157); $\nu_{max.}$(Nujol) 3 400 (N–H), 2 245 (C≡N), and 800 cm^{-1} (1,2,4-trisubstitution); $\delta_H(CDCl_3)$ 7.38—7.07 (3 H, m, Ar), 3.82 (2 H, s, CH_2), and 2.72 and 1.92 (4 H each, m, cyclic CH_2).

Attempted Preparation of 6-Cyanomethyl-N-methyl-1,2,3,4-tetrahydrocarbazole (10). [*Preparation of* (12)].—6-Cyanomethyltetrahydrocarbazole (0.8 g, 0.0038 mol) was treated with an excess of methyl iodide in sodamide–liquid ammonia; yield of (12) 70%, m.p. 89—90 °C; $\nu_{max.}$(Nujol) 2 240 (CN) and 800 cm^{-1} (1,2,4-trisubstitution); M^+, *m/e* 252 (Calc. for $C_{15}H_{16}N_2$: 224). See preparation of corresponding hexahydrocarbazole.

Preparation of 6-Cyanomethyl-N-methyl-1,2,3,4-tetrahydrocarbazole (10).—*p*-*N*-Methylaminobenzyl cyanide was condensed with 2-chlorocyclohexanone using the Bischler reaction as previously described. The crude product was extracted with ether and recrystallised from light petroleum (b.p. 60—80 °C); yield 20%, m.p. 84—85 °C; M^+, *m/e* 224 (Calc. for $C_{15}H_{16}N_2$: 224); $\nu_{max.}$(Nujol) 2 235 (C≡N), 1 615 and 1 580 (C=C), and 800 cm^{-1} (1,2,4-trisubstitution); $\delta_H(CDCl_3)$ 7.39—6.94 (3 H, m, Ar), 3.78 (2 H, s, CH_2), 3.56 (3 H, s, N–CH_3), and 2.69 and 1.88 (4 H each, m, cyclic CH_2).

Substituted 1,2,3,4,4a,9a-Hexahydrocarbazoles.—The method used for the hydrogenation of tetrahydrocarbazoles in ethanol–aqueous fluoroboric acid solution has been described.[2a,6] The analysis, by g.l.c., of isomer mixtures used a Perkin-Elmer F11 instrument with 10 or 15% Carbowax 20M on Chromosorb P columns. For the 3-substituted derivatives the major, *cis,syn*-isomer was isolated using preparative scale g.l.c. on a Varian-Aerograph A90P instrument with a 10% Carbowax 20M on Chromosorb P column.

syn-3-*Substituted 9-Methyl-1,2,3,4,4a,9a-cis-hexahydrocarbazoles.*—*3-Hydroxymethyl:* b.p. 142—145 °C/0.1 mmHg; $\nu_{max.}$(film) 3 350 (broad, hydrogen-bonded OH), 2 800 (N–Me), 1 610 (C=C, Ar), and 750—740 cm^{-1} (d, 1,2-disubstitution); $\delta_H(CDCl_3)$ 7.23—6.48 (4 H, m, Ar), 3.43 (2 H, d, CH_2), and 2.69 (3 H, s, N–CH_3) (Found: C, 77.15; H, 8.65; N, 6.25. $C_{14}H_{19}NO$ requires C, 77.38; H, 8.81; N, 6.45%).

3-Methoxymethyl: b.p. 123—125 °C/0.05 mmHg; $\nu_{max.}$(film) 1 610 (C=C, Ar), 1 120 (C–O–C, acyclic ether), and 755—735 cm^{-1} (1,2-disubstitution); $\delta_H(CDCl_3)$ 7.22—6.42 (4 H, m, Ar), 3.29 (3 H, s, O–CH_3), 3.12 (2 H, d, –CH_2), and 2.67 (3 H, s, N–CH_3) (Found: C, 78.3; H, 9.0; N, 6.15. $C_{15}H_{21}NO$ requires C, 77.92; H, 9.09, N, 6.06%).

3-Cyanomethyl: b.p. 130—132 °C/0.05 mmHg; $\nu_{max.}$(film) 2 240 (C≡N), 1 610 (C=C, Ar), and 755—740 cm^{-1} (1,2-disubstitution); $\delta_H(CDCl_3)$ 7.31—6.49 (4 H, m, Ar), 2.64 (3 H, s; N–CH_3), and 2.12 (2 H, d, –CH_2CN) (Found: C, 79.5; H, 8.05; N, 12.05. $C_{15}H_{18}N_2$ requires C, 79.64; H, 7.06; N, 12.38%).

6-Substituted 9-Methyl-1,2,3,4,4a,9a-cis-hexahydrocarbazoles.—*6-Ethoxycarbonyl.* The corresponding tetrahydrocarbazole was hydrogenated in the usual way except for the addition of dioxan to aid dissolution; yield 60%, b.p. 220—225 °C at 0.5 mmHg; g.l.c. showed two components in the ratio 97.5 : 2.5; $\nu_{max.}$(film) 1 705 (C=O, benzoate), 1 615 (C=C, Ar), and 775 cm^{-1} (1,2,4-trisubstitution); M^+, *m/e* 259.1567 ($C_{16}H_{21}NO_2$ requires *m/e*, 259.1572); $\delta_H(CDCl_3)$ 7.85—6.34 (3 H, m, Ar), 4.25 (2 H, q, J = 7 Hz, CH_2), 2.74 (3 H, s, N–CH_3), and 1.35 (3 H, t, J = 7 Hz, –CH_3).

6-Hydroxymethyl. The corresponding 6-ethoxycarbonyl-9-methylhexahydrocarbazole was reduced using lithium aluminium hydride in dry ether; yield 60%; g.l.c. showed two components in the ratio 98 : 2. The major (*cis*) isomer was isolated by fractional distillation; b.p. 141—143 °C/0.1 mmHg; $\nu_{max.}$(film) 3 350 (broad, hydrogen-bonded OH), 1 615 (C=C, Ar), and 805 cm^{-1} (1,2,4-trisubstitution);

$\delta_H(CDCl_3)$ 7.05—6.36 (3 H, m, Ar), 4.45 (2 H, s, CH_2), 3.58 (1 H, t, *J ca.* 5 Hz), 2.92 (1 H, q, *J ca.* 6 Hz), 2.65 (3 H, s, N–CH_3), and 2.36 (1 H, OH) (Found: C, 77.4; H, 8.9; N, 6.0. $C_{14}H_{19}NO$ requires C, 77.59; H, 8.81; N, 6.45%).

6-*Methoxymethyl*. The attempted hydrogenation of 6-methoxymethyl-*N*-methyltetrahydrocarbazole yielded a solid product with m.p. 120—170 °C. The i.r. and n.m.r. spectra gave no evidence for the methoxy-group, indicating that the ether link had been cleaved. The mass spectrum showed three identifiable molecular ions: *m/e* = 229, the unchanged starting material; *m/e* = 199, 6-methyl-*N*-methyltetrahydrocarbazole ($C_{14}H_{17}N$); and *m/e* = 201, 6-methyl-*N*-methylhexahydrocarbazole ($C_{14}H_{19}N$). It was, therefore, assumed that rapid hydrogenolysis had taken place.

The successful preparation entailed methylation of the hydroxymethyl compound as described for the corresponding 3-substituted derivative. The major (*cis*) isomer was isolated by fractional distillation; b.p. 128—130 °C at 0.1 mmHg; $\nu_{max.}$(film) 1 615 (C=C, Ar), 1 095 (C–O–C, acyclic ether), and 800 cm^{-1} (1,2,4-trisubstitution); $\delta_H(CDCl_3)$ 7.09—6.41 (3 H, s, Ar), 4.35 (2 H, s, CH_2), 3.35 (3 H, s, O–CH_3), and 2.67 (3 H, s, N–CH_3); M^+, *m/e* 231.1626. $C_{15}H_{21}NO$ requires 231.1623.

6-(1-*Cyano*-1-*methylethyl*). The product obtained from the methylation of 6-cyanomethyltetrahydrocarbazole (see above) was hydrogenated in the usual way; g.l.c. showed only one component; yield 60%, b.p. 148—150 °C/0.1 mmHg; $\nu_{max.}$(film) 2 240 (CN), 1 608 (C=C, Ar), and 790 cm^{-1} (1,2,4-trisubstitution); $\delta_H(CDCl_3)$ 7.23—6.41 (3 H, m, Ar), 3.22 (1 H, q, *J ca.* 6 Hz), 2.99 (1 H, t, *J ca.* 6 Hz), 2.69 (3 H, s, N–CH_3), and 1.68 (6 H, s); M^+, *m/e* 254 ($C_{17}H_{22}N_2$ requires *m/e* 254) (Found: C, 80.85; H, 8.85; N, 11.15. $C_{17}H_{22}N_2$ requires C, 80.31; H, 8.66; N, 11.02%).

6-*Cyanomethyl*. The hydrogenation of the corresponding tetrahydrocarbazole in ethanol–fluoroboric acid (42% w/w), with the addition of a minimum of dioxan to aid dissolution, gave a mixture of isomers of the required compound (98% : 2%). The major (*cis*) isomer was obtained by fractional distillation; yield 50%, b.p. 170—172 °C at 0.1 mmHg; $\nu_{max.}$(film) 2 240 (C≡N), 1 610 (C=C, Ar), and 805 cm^{-1} (1,2,4-trisubstitution); $\delta_H(CDCl_3)$ 7.12—6.38 (3 H, m, Ar), 3.61 (2 H, s, CH_2CN), 3.25 (t) and 3.05 (g) (1 H each, probably ring-fusion protons), 2.69 (3 H, s, N–CH_3) (Found: C, 79.9; H, 8.15; N, 12.1. $C_{15}H_{18}N$ requires C, 79.60; H, 8.02; N, 12.38%).

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