Synthesis of 1,2,3,4-Tetrahydrocarbazoles with Large Groups — Aromatization to Carbazoles[1]

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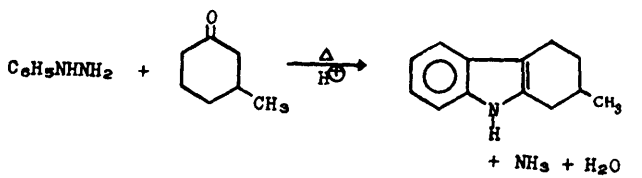
Tetrahydrocarbazoles can be prepared from cyclohexanone and phenylhydrazines as illustrated by the one-step synthesis of Rogers and Corson (1947).



These compounds can be aromatized by heating with chloranil in xylene (Barclay and Campbell, 1945) and reduced electrolytically to the cis-hexahydro derivatives (Perkin and Plant, 1924) or over metal catalysts to the dodecahydro (Elderfield, 1952) derivatives, all in high yield.

Few hexahydrocarbazoles — and fewer dodecahydrocarbazoles — are known. These compounds, like several substituted carbazoles (Clayson, 1962), may be biologically active. For this latter possibility, for the purpose of studying the nuclear magnetic resonance spectra of these compounds and to explore the possibilities of the Rogers-Corson type of Fischer indole synthesis, conformationally rigid ketones, 4-*t*-butylcyclo-

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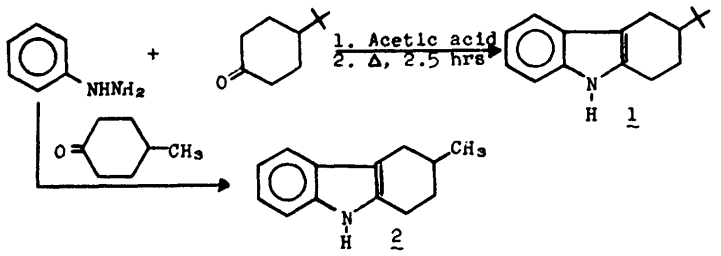
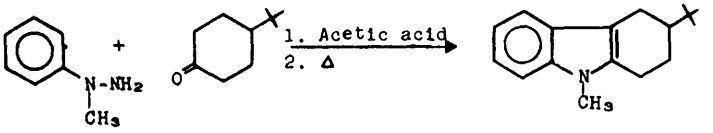
hexanone and 2-cyclohexylcyclohexanone, were examined. It was thought that this type of ketone would provide a polyhydrocarbazole more resistant to air oxidation because of steric factors. 3-*t*-Butyl-1,2,3,4-tetrahydrocarbazole (1) and 3-methyl-1,2,3,4-tetrahydrocarbazole (2) were prepared, the latter compound to serve as a model in proof of structure for 1, which is new. Both 1 and the methyl compound 2 showed infrared bands for N-H, at about 3400 cm^{-1} and 3350 cm^{-1} respectively.

The yield of 3-*t*-butyl-1,2,3,4-tetrahydrocarbazole (1) was 81.1%.



Elemental and infrared (IR) analysis support the structure for 1, as does the nuclear magnetic resonance (NMR) spectrum.

1-Methyl-1-phenylhydrazine reacted with 4-*t*-butylcyclohexanone to



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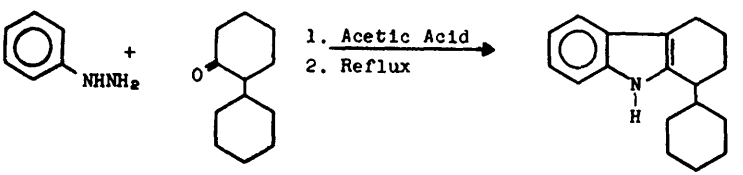
give 3-*t*-butyl-N-methyl-1,2,3,4-tetrahydrocarbazole (3). The same method was employed as was used for 1 except that the reaction was run for 5 hr; yield, 78.8%. When the reaction proceeded for only 2.5 hr, a low yield (27.4%) was realized. Elemental analysis supports the structure for 3.



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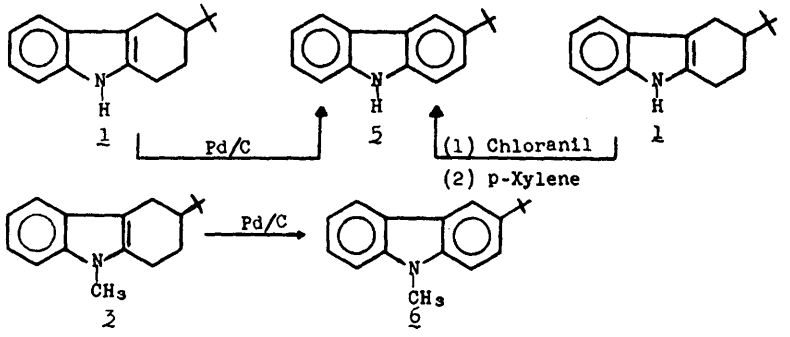
The yield of 1-cyclohexyl-1,2,3,4-tetrahydrocarbazole (4) from phenylhydrazine and 2-cyclohexylcyclohexanone was low (28.5%) even when the reaction mixture was boiled for 10 hr. Evidently the cyclohexyl group of 2-cyclohexylcyclohexanone hinders formation of 4. Elemental and IR analyses supports the structure of 4. Gas-liquid chromatography (GLC) analysis of a solution of 4 in ether showed the compound to be pure. Unfortunately, low solubility of 4 in a wide range of organic solvents prevented taking an NMR spectrum.

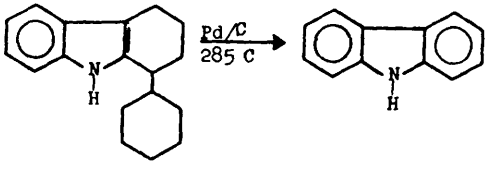
Dehydrogenation of 1 and 3 gave 5 and 6, respectively, and proceeded

in nearly quantitative yields. However, when 1 was dehydrogenated with chloranil (Barclay and Campbell, 1945) only a very small amount of 5 was recovered after column chromatography on alumina. The elemental and IR analyses as well as the NMR spectra support the structures of 5 and 6.



Dehydrogenation of 4 was attempted by heating the compound with palladium on charcoal at 215 C for 2 hr. This reaction was found to proceed most smoothly when glass helices were added to prevent bumping. Products melting at 93-93.5 C (P-1), 83.5-84 C (P-2), and 122.5-123 C (P-4) could be isolated via column chromatography, all in low yield. NMR (in CCl_4) and IR analyses gave indication that aliphatic protons were present in each product. Elemental analysis confirmed that dehydrogenation had not been complete in P-1, P-2, and P-4. Elemental and NMR analyses indicated P-4 to have the structure of 1-cyclohexylcarbazole, thus only partial aromatization occurred in the molecular system.

A similar dehydrogenation was performed at 285 C. An appreciable amount of dealkylation apparently occurred, since carbazole was found in the products via chromatography on alumina of the reaction mixture, but much starting material could be recovered, also.



+ several other products

Besides carbazole this reaction gave several low-melting unidentified products in very low yield. The other major product, besides carbazole, was a white crystalline solid (P-3) melting at 193.8-194.3 C. An NMR (in CCl_4) spectrum showed only aromatic protons; another proton, apparently N-H, was obscured by noise but integration established its presence. Although GLC indicated P-3 to be pure, elemental analysis did not give the results to be expected for 1-phenylcarbazole, $C_{18}H_{13}N$. The molecule appears to have a complicated structure.

Thus it appears that a large group in the 4-position of the starting cyclohexanone does not inhibit the condensation and a stable tetrahydro product is formed; aromatization to the carbazole is facile. In contrast, a large group in the 2-position of the cyclohexanone retards the condensation and creates a steric barrier to aromatization to the substituted carbazole. Loss of the cyclohexyl group is a serious side reaction if the dehydrogenation of 4 is performed over a palladium catalyst.

EXPERIMENTAL

Analytical methods—Melting points are uncorrected. The NMR spectra were recorded on a Varian A-60 high resolution spectrometer with tetramethylsilane as the internal standard. A Beckman IR-5A infrared spectrometer was used to record the infrared spectra. An Aerograph A-550 Hy F1 unit was used for GLC analysis. Elemental analyses were performed by Galbraith Labs, Inc., Knoxville, Tennessee.

Preparation of 3-t-Butyl-1,2,3,4-tetrahydrocarbazole (1)—By the method of Rogers and Corson (1947) phenylhydrazine (21.6 g, 0.200 mole) was added during 1 hr to a boiling solution of 4-*t*-butylcyclohexanone (30.9 g, 0.200 mole) in glacial acetic acid (72.0 g, 1.20 mole). The resulting mixture was held at reflux for 2.5 hr after the addition was complete. The reaction mixture was cooled to room temperature and then to 0 C in an ice-water bath. A granular, tan solid precipitated and was filtered out and washed successively with about 30 ml of water and methanol; yield, 37 g (81.1%); mp 128.1-128.8 C; IR absorption maxima: 3400 (N-H), 3000-2600 (C-H), 1440-1410 (C-CH_2), 1380 and 1370 [C-$(CH_3)_3$], 1335 and 741 cm^{-1} (ortho substitution); NMR δ 6.85 (multiplet-aromatic hydrogen), 2.40 (multiplet), 2.00 (multiplet) and 0.96 (singlet-methyl group).

Analysis: $C_{16}H_{21}N$; Calculated: C. 84.53; H, 9.31; N, 6.16. Found: C, 84.30; H, 9.15 N, 6.43.

Preparation of 3-t-Butyl-N-methyl-1,2,3,4-tetrahydrocarbazole (3)—The method of preparation was the same as for *t*-butyl-1,2,3,4-tetrahydrocarbazole except that the reaction was run for 5 hr. The reagents used were 1-methyl-1-phenylhydrazine (10.0 g, 0.08 mole), 4-*t*-butylcyclohexanone (12.2 g, 0.08 mole) and glacial acetic acid (30 g, 0.50 mole). The crystals isolated weighed 15.5 g (78.8%); mp 66.5-67.5 C.

Analysis: $C_{17}H_{23}N$; Calculated: C, 84.59; H, 9.60; N. 5.80. Found: C, 84.62; H, 9.56; N, 5.82.

Preparation of 1-Cyclohexyl-1,2,3,4-tetrahydrocarbazole (4)—This compound was prepared using the method of Rogers and Corson (1947) in the one-step synthesis of 1,2,3,4-tetrahydrocarbazoles also. To a boiling solution of 2-cyclohexylcyclohexanone (180.3 g, 1.00 mole) and glacial acetic acid (360.0 g, 6.00 moles), phenylhydrazine was added dropwise during 1 hr. After being stirred at the boiling point for an additional 10 hr, the mixture was cooled to room temperature. Crystals did not form even at 5 C. Therefore the acetic acid was diluted by adding ether (400 ml) as additional solvent and neutralized with solid sodium bicarbonate; this was followed by washing the solution with a saturated solution of sodium bicarbonate (200 ml), and finally with distilled water. The mixture was dried ($MgSO_4$) and the ether was evaporated; this left a dark heavy oil. From this oil, crystals began to form. Attempted solution of the oil in methanol (200 ml) accelerated the crystallization process. The yield was 72.3 g (28.5%). Recrystallization from methanol (or CH_3CN) gave white crystals, m p 115.0-117.0 C. GLC analysis with ether as a solvent on a 5% silicone rubber column showed the product to be pure. IR absorption maxima occurred at 3300 (N-H), 2950, 1600, 775, 755, and 735 cm^{-1}. The compound appears to oxidize on standing in air.

Analysis: C_{18} $H_{23}N$; Calculated: C, 85.32; H, 9.15; N, 5.53. Found: C, 85.37; H, 9.33; N. 5.23.

Preparation of 3-t-Butylcarbazole (5)—A freshly prepared mixture of *t*-butyl-1,2,3,4-tetrahydrocarbazole (10.0 g) and palladium on charcoal (1.02 g) was heated to boiling (163 C) under dry nitrogen. The mixture was boiled an additional 2.5 hr, with the temperature at 190 C the last 0.5 hr, and was then allowed to cool to room temperature. The mixture was

dissolved in benzene, and the charcoal was filtered off with the aid of celite. After partial purification from benzene, the solid was recrystallized from methanol, mp 151-152 C; IR absorption maxima were visible at 3420 (N-H), 3000 and 2900 (aromatic and aliphatic C-H), 855, 820, 773, and 755 cm^{-1}; NMR δ 8.13, 7.38, 1.42.

Analysis: $C_{16}H_{17}N$; Calculated: C, 86.05; H, 7.67. Found: C, 85.82; H, 7.67.

By the method of Barclay and Campbell (1945) 3-*t*-butyl-1,2,3,4-tetrahydrocarbazole (1.62 g, 0.007 mole) and chloranil (3.50 g, 0.142 mole) were heated to reflux in xylene (30.0 ml) until a few drops of the solution gave no red color when heated with sodium hydroxide (24.5 hr). The reaction solution was then cooled, separated from tetrachlorohydroquinone, diluted with xylene, shaken first with 0.1 N sodium hydroxide three times and then with water, and finally dried (Na_2SO_4). On evaporation of xylene, impure crystals deposited and were purified by chromatography on alumina using a 1:1 benzene-Skelly F and ether combination for elution. A low yield of pure crystals was obtained, mp 149.3-151 C; mixture melting point determination showed it identical to 5 previously obtained.

Preparation of t-Butyl-N-methylcarbazole (6)—The method was the same as that used to produce *t*-butylcarbazole except that the reaction temperature was 135 C. After 2 hr the temperature had risen to 156 C. The materials used were 3-*t*-butyl-N-methyl-1,2,3,4-tetrahydrocarbazole (10 g) and palladium on charcoal (1 g). The mixture was allowed to cool to room temperature, the resulting solid dissolved in acetonitrile, and the charcoal filtered off with the aid of celite. Crystals were recovered from the oil left after evaporation of acetonitrile; crude yield, 8.78 g (89.0%). Separation of crystals from impurities was accomplished via chromatography on alumina; mp 51.5-52.8 C; IR maxima, 2880 and 2990 (aliphatic and aromatic C-H), 870, 805 and 770 cm^{-1}; NMR δ 8.05 to 7.05 (aromatic H), 3.45 (CH_3) and 1.40 (*t*-butyl).

Analysis: $C_{17}H_{19}N$; Calculated: C, 86.03; H, 8.06; N, 5.90. Found: C, 85.75; H, 8.08; N, 5.93.

Dehydrogenation of 4—Fifteen g of 4 (mp 114-117 C) was mixed in a 250-ml, three-necked flask (equipped with a condenser, thermometer and nitrogen inlet) with 2 g of palladium on charcoal. Glass helices were put into the reaction vessel to increase the reaction surface. The mixture was heated slowly until the temperature reached 285 C; then it was held at that temperature for 1 hr. The mixture was cooled and 100 ml of 1:1 benzene-ether solution was added to prevent the melt from hardening. After the solvent was partially removed, crystals began to form. These crystals were recrystallized from CCl_4 and identified as carbazole, mp 243-244 C. GLC analysis of the residual oil (obtained from evaporation of the ether) showed the presence of seven components. Column chromatography of the oil over alumina using *n*-hexane and ether for elution solvents gave only partial separation of components. A product (0.5 g of P-3) was found to melt at 193.8-194.3 C after recrystallization from methanol; IR absorption maxima, 1430 and 1775 cm^{-1}, NMR δ 7.6 (multiplet) and another broad peak buried in the noise (probably N-H). When the dehydrogenation was attempted at 215 C, P-1, P-2 and P-4 were fractionally crystallized from the mixture. The NMR spectrum of P-4 in CCl_4 showed signals at δ 6.85-8.0 (8 protons), 2.49-2.90 (1 proton and 1.08-2.18 (10 protons) which corresponds to the structure of 1-cyclohexylcarbazole. Apparently, the signal for the tertiary proton is buried under those of the aromatic protons.

Analysis: $C_{18}H_{13}N$; Calculated: C, 88.86; H, 5.39 (for 1-phenylcarbazole).
$C_{18}H_{19}N$; Calculated: C, 86.70; H, 7.68; N, 5.62 (for 1-cyclohexylcarbazole). Found: P-1, C, 83.44; H, 9.59; N, 6.20. P-2, C, 83.81; H, 9.66; N, 6.67. P-3, C, 90.72; H, 5.13. P-4, C, 86.63; H, 7.68; N, 5.82.

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