# An Alternative Synthesis of 3-Amino-1,2,3,4-tetrahydrocarbazoles



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3-Amino-1,2,3,4-tetrahydrocarbazoles are easily prepared from the readily available 3-hydroxy-1,2,3,4-tetrahydrocarbazoles by conversion of the latter to the *p*-toluene- or methanesulfonate ester, followed by nucleophilic displacement with azide ion. The resulting 3-azido-1,2,3,4-tetrahydrocarbazoles are then catalytically hydrogenated to their 3-amino counterparts.

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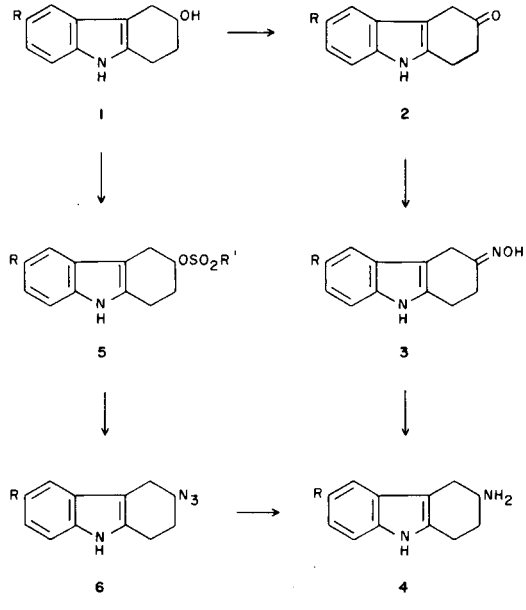
3-Amino-1,2,3,4-tetrahydrocarbazoles **4** are of pharmacological interest since they can be regarded as tryptamine analogues with a clearly defined spatial relationship between the amino group and the indole nucleus.

Although compound **4** (R = H) has been obtained [1] in low yield by partial hydrogenation of 3-aminocarbazole, the only general synthesis [2] of these compounds reported so far entails successive oximation and reduction of the appropriate 1,2-dihydrocarbazol-3(4*H*)-one **2**. However, the production of such ketones by the oxidation of the corresponding alcohols **1** has proved problematical [2,3]. In our experience the recommended [2] Opennauer oxidation procedure has also proved unsatisfactory and better, though modest, yields of ketone are obtained with *N,N'*-dicyclohexylcarbodiimide and phosphoric acid in dimethyl sulphoxide. The present communication describes an alternative route to 3-amino-1,2,3,4-tetrahydrocarbazoles.

The method depends upon conversion of the corresponding 3-hydroxy-1,2,3,4-tetrahydrocarbazole **1** to its *p*-toluenesulphonate or methanesulphonate ester **5** followed by displacement with sodium azide in dimethyl sulphoxide to give the 3-azido compound **6**. The latter compound is then reduced with hydrogen over palladised charcoal to give the 3-amino-1,2,3,4-tetrahydrocarbazole **4**. Each of the steps proceeds in good yield so that in the case of the rather sensitive 6-methoxy compounds the whole sequence of reactions can be carried out without purification of the intermediates.

Although an anomalous nucleophilic displacement pathway has been observed [4,5] in related indolic systems which could have resulted in the formation of the isomeric 4-amino-1,2,3,4-tetrahydrocarbazoles, careful scrutiny has failed to detect its intervention in the present cases. The amine **4**, R = H was identical with material obtained by the original route and the structure of the newly synthesised 6-methoxy derivative **4**, R = MeO is unambiguously established by its $^1$H nmr spectrum. In particular, the H-4 protons are observed as double doublets at δ 2.43 and 2.97 ($J_{gem}$ = 15 Hz) as a consequence of coupling with H-3, observed as a multiplet at δ 3.20-3.35, with $J_{H3,H4}$ = 6.7 and 5.1 Hz respectively.




## EXPERIMENTAL

Nuclear magnetic resonance ($^1$H nmr) spectra were recorded on a Perkin-Elmer R12B spectrometer at 60 MHz or a Nicolet NT200 spectrometer at 200 MHz and are reported in parts per million downfield from tetramethylsilane as an internal standard. Infrared (ir) spectra, reported in reciprocal centimetres, were recorded on a Pye-Unicam SP200 or on a Perkin-Elmer 157 spectrometer. Melting points were obtained using a Gallenkamp melting point apparatus and are uncorrected.

3-Amino-1,2,3,4-tetrahydrocarbazole.

3-Hydroxy-1,2,3,4-tetrahydrocarbazole [2] was converted to its *p*-toluenesulphonate ester by reaction with *p*-toluenesulphonyl chloride in pyridine at room temperature, yield 88%, mp 151-152° dec (from toluene); ir (Nujol) 3400, 1590, 1340, 1180, 1160, 870, 760, 720 cm$^{-1}$; $^1$H-nmr (DMSO-$d_6$): 60 MHz, 1.80-2.15 (m, 2H, H-2), 2.40 (s, 3H, $CH_3$), 2.50-2.90 (m, 4H, H-1 and H-4), 4.90-5.10 (m, 1H, H-3), 6.95-7.35 (m, 4H, ArH), 7.55 (d, 2H, J = 8.0 Hz, H-2'), 7.95 (d, 2H, J = 8.0 Hz, H-3') ppm.

*Anal.* Calcd. for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 67.05; H, 5.66; N, 4.09.

The *p*-toluenesulphonate (0.7 g) and sodium azide (0.21 g) in dry dimethylsulphoxide (20 ml) were heated under nitrogen on a steam-bath for 24 hours. The cooled reaction mixture was poured into water and extracted with ether. The extracts were washed with water, dried (sodium sulfate) and evaporated to give the crude azide (0.35 g); ir: ν max 3400, 2100 cm$^{-1}$. This material was dissolved in methanol (50 ml) and hydrogenated

in the presence of 10% palladised charcoal (50 mg) at 60 psi and room temperature for 24 hours. The filtered solution was then evaporated and the 3-amino-1,2,3,4-tetrahydrocarbazole sublimed at 180°/0.1 torr; yield 0.2 g (52%), mp 176-177° ref [1] mp 170-172°; ir (Nujol): 3350, 3200, 3100, 1610, 1590, 770, 750 $cm^{-1}$; $^1$H-nmr (acetone-$d_6$): 60 MHz, 1.73 (s, 2H, $NH_2$), 1.85-2.0 (m, 2H, H-2), 2.52-2.94 (m, 4H, H-1 and H-4), 3.68-3.95 (m, 1H, H-3), 6.80-7.16 (m, 2H, H-6 and H-7), 7.20-7.43 (m, 2H, H-5 and H-8), 9.64 (bs, 1H, NH) ppm.

*Anal.* Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.0; H, 7.34; N, 15.40.

3-Benzoyloxy-6-methoxy-1,2,3,4-tetrahydrocarbazole.

4-Benzoyloxycyclohexanone [5] (9.5 g) and *p*- methoxyphenylhydrazine were condensed in boiling ethanol (10 ml) containing a few drops of acetic acid. After 10 minutes the ethanol was evaporated *in vacuo* and acetic acid (200 ml) added to the residue. The mixture was refluxed under nitrogen for 4 hours and then evaporated *in vacuo*. Aqueous 2*M* sodium hydroxide (100 ml) was added to the residue and the crude indole obtained by extraction with dichloromethane. The red oil thus obtained was chromatographed over silica gel in dichloromethane to give 3-benzoyloxy-6-methoxy-1,2,3,4-tetrahydrocarbazole, yield 6.6 g (47%) mp 138-140° (from ethanol); ir (Nujol): 3350, 1700, 1620, 1600, 820, 810, 710 $cm^{-1}$; $^1$H-nmr (deuteriochloroform): 200 MHz, 2.15-2.30 (m, 2H, H-2), 2.80-3.00 (m, 2H, H-1), 2.97 (d d, 1H, J = 16.2 and 6.4 Hz, H-4), 3.20 (d d, 1H, J = 16.2 and 5.0 Hz, H-4), 3.84 (s, 3H, $OCH_3$), 5.56 (q, 1H, J's = 5 Hz, H-3), 6.80 (d d, 1H, J = 8.7 and 2.3 Hz, H-7), 6.91 (d, 1H, J = 2.3 Hz, H-5), 7.19 (d, 1H, J = 8.7, H-8), 7.41 (t, 2H, J = 7.0 Hz), 7.55 (d, 1H, J = 7.0 Hz), 7.73 (b s, 1H, NH), 8.05 (d, 2H, J = 7.0 Hz) ppm.

*Anal.* Calcd. for $C_{20}H_{18}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.65; H, 6.01; N, 4.31.

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole.

3-Benzoyloxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (5.6 g) and potassium hydroxide (1.9 g) in water (17.5 ml) and ethanol (250 ml) were heated under reflux in a nitrogen atmosphere for 6 hours. The ethanol was evaporated *in vacuo* and the residue partitioned between dichloromethane and water. The dichloromethane extract was dried (sodium sulfate) and evaporated to give the crude alcohol; ir (dichloromethane): 3350-3200, 1620, 1600 $cm^{-1}$; $^1$H nmr (chloroform): 60 MHz, 1.60-2.00 (m, 2H, H-2), 2.30-2.90 (m, 4H, H-1 and H-4), 3.00 (bs, 1H, OH), 3.90-4.30 (m, 1H, H-3), 6.75 (d d, 1H, J = 8.5 and 3.0 Hz, H-7), 6.85 (d, 1H, J = 3.0 Hz, H-5), 7.00 (d, 1H, J = 8.5 Hz, H-8), 8.08 (b s, 1H, NH) ppm.

A stirred solution of the alcohol (3.5 g) in ice-cold pyridine (30 ml) was treated dropwise with methanesulphonyl chloride (1.14 ml) and the mixture allowed to stand for 24 hours. Most of the pyridine was evaporated *in vacuo* and the residue partitioned between dichloromethane and water. The dichloromethane extract was washed successively with aqueous 2*M* sulphuric acid and water, dried (sodium sulfate) and evaporated to give the mesylate as an oil; ir (neat): 3350, 1620, 1600, 1350, 1190, 1160 $cm^{-1}$; $^1$H-nmr (deuteriochloroform): 60 MHz, 1.90-2.30 (m, 2H, H-2), 2.40-3.10 (m, 4H, H-1 and H-4), 2.90 (s, 3H, $CH_3SO_3$-), 3.80 (s, 3H, $CH_3O$), 4.90-5.20 (m, 1H, H-3), 6.75 (d d, 1H, J = 8.5 and 3.0 Hz, H-7), 6.85 (d, 1H, J = 3.0 Hz, H-5), 7.10 (d, 1H, J = 8.5 Hz, H-8), 8.0 (b s, 1H, NH) ppm.

The mesylate (4.0 g) and sodium azide (0.72 g) in dry dimethyl sulphoxide (30 ml) under nitrogen were stirred and heated on a steam-bath for 10 hours. The cooled reaction mixture was poured into water and the azide isolated by ether extraction. The oily azide (2.5 g, $\nu$ max 2100 $cm^{-1}$) was dissolved in methanol (50 ml) and hydrogenated at room temperature and 50 psi pressure for 24 hours in the presence of 10% palladised charcoal (0.1 g). The resulting solution was filtered and evaporated *in vacuo*. The residue was then partitioned between ether and aqueous 2*M* hydrochloric acid. The acid extracts were then basified with aqueous 2*M* sodium hydroxide and the 3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole isolated by extraction with dichloromethane yield 1.0 g (26% overall), mp 118-120° (from benzene petroleum ether); ir (Nujol): 3350, 3250, 3150, 1620, 1600, 850, 820, 750 $cm^{-1}$; $^1$H-nmr (deuteriochloroform): 200 MHz, 1.50 (b s, 2H, $NH_2$), 1.69-1.85 (m, 1H, H-2), 1.90-2.10 (m, 1H, H-2), 2.43 (d d, 1H, J = 15.0 and 6.7 Hz, H-4), 2.72-2.81 (m, 2H, H-1), 2.97 (d d, 1H, J = 15.0 and 5.1 Hz, H-4), 3.20-3.35 (m, 1H, H-3), 3.84 (s, 3H, $CH_3O$), 6.52 (d d, 1H, J = 8.6 and 2.4 Hz, H-7), 6.85 (d, 1H, J = 2.4 Hz, H-5), 7.13 (d, 1H, J = 8.6 Hz, H-8), 7.88 (b s, 1H, NH) ppm.

*Anal.* Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.08; H, 7.39; N, 12.83.

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