Intermediates for the Synthesis of Tetracyclic Indole Alkaloids. Synthesis of 4-Aminotetrahydrocarbazole Derivatives

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An efficient method for the synthesis of 4-aminotetrahydrocarbazole derivatives from 2,3-dihydrospiro-[1*H*-carbazole-1,2'-(1,3)-dithiolan]-4-(9*H*)-one **1** is described. The structure of compound **6** has been confirmed by X-ray structure analysis.

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Our interest in this study is the preparation of 4-aminotetrahydrocarbazole derivatives, having an activated side chain on the N_b-group and a keto-group at position 1 (carbazole numbering). These types of compounds allow synthesis of tetracyclic indole alkaloids skeleton from 1-oxo-1,2,3,4-tetrahydrocarbazoles. One of the compounds has been converted to azocino[4,3-*b*]indole by a novel type of ring closure [1]. The first synthesis of 4-acetaminotetrahydrocarbazole and 4-aminohexahydrocarbazole derivatives were reported by Fritz [2]. Recently, we synthesized the same type of compounds which involves a keto-group at position 1 of tetrahydrocarbazole successfully [3]. We used 4-oxotetrahydrocarbazole as a starting material and synthesized the corresponding oximes which were converted to amide derivatives by catalytic hydrogenation. So far, the 4-amino compounds which have free amine groups have not been isolated. These types of amines were trapped succesfully. In this study we started from a 4-oxotetrahydrocarbazole derivative which was reacted to produce imine. 4-Amino-substituted tetrahydrocarbazole derivatives were obtained by reduction of the corresponding imines using sodium borohydride. Sulfonamide **6** was formed from **4** [4] by the reaction with benzenesulfonyl chloride and triethylamine in chloroform. The structure of **6** was determined by X-ray structure analysis (Figures 1 and 2). The benzamide **7** was obtained by treatment of **4** with benzoyl chloride and triethylamine in chloroform. In order to remove the protecting group from **7** we have tried all the methods given in the literature [5]. However, only one of these methods was successful. We used benzeneseleninic anhydride, pyridine in chloroform, to remove the protecting group from **7** and thus **9** was obtained. Unfortunately, all the attempts to cleave the ether group [6] from **9**, to obtain the desired alcohol **11**, failed and only decomposition products were obtained.

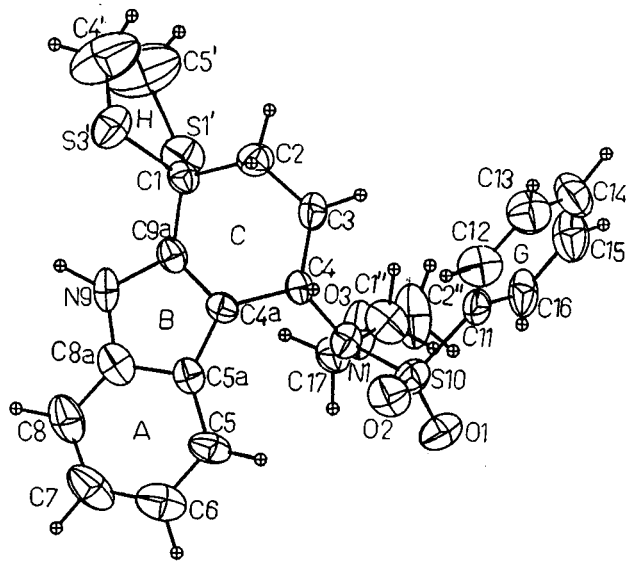


Figure 1. X-Ray crystal structure of compound **6**.

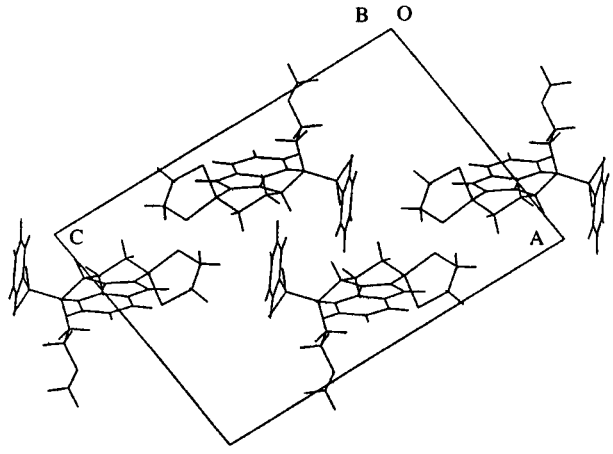
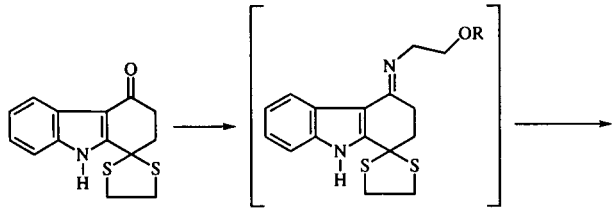


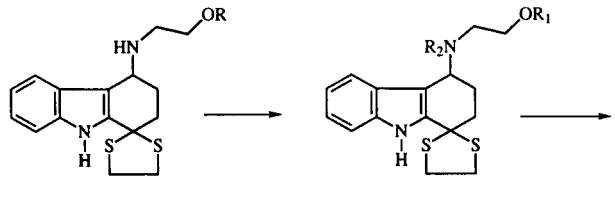
Figure 2. a-c projection of crystal packing of **6**.

Therefore, we selected a different synthetic route. Compound **1** [7] was treated with 2-benzyloxyethylamine to give the unstable imine **3** by using ferric chloride as a catalyst. Without isolation of **3**, we reduced it using sodium borohydride [8]. Acylation of intermediate **5** with benzoyl chloride gave the corresponding amide **8**. Removal of the protecting group from **8** with benzeneseleninic anhydride yielded ketone **10**. In the next step, compound **10** was hydrogenated with palladium hydroxide [9] to give the known alcohol **11**.

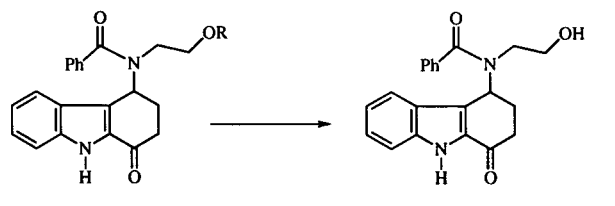
Crystal Data for **6** $C_{23}H_{26}N_2O_3S_3$ is: M_r = 474.65, F(000) = 1000, monoclinic, a = 12.992 (4), b = 9.610(3), c = 18.706(4) Å, β = 98.90(3)°, V = 2307.4 (1.1) A^3, space group $P2_1/c$, Z = 4, D_x =1.366 Mg m^{-3} μ = 0.33 mm^{-1}. The experimental data were collected at room temperature on an Enraf-Nonius CAD-4 diffractometer with MoK_α radiation (λ = 0.71069 Å). The structure was solved by direct methods. The final R value was 0.039 (R_W = 0.041). H atoms were geometrically positioned 1.0 Å from the corresponding atoms and a riding model was used in the refinement process. Initially a unit weighting scheme was used, but in the final stages of the refinement the weights were assigned using the method described by Carruthers and Watkin [10], as incorporated into the CRYSTALS package of programs [11]. Programs used were CRYSTALS, SHELXS86 [12] and SNOOPI [13].



1 **2** R: CH_3 **3** R: $PhCH_2$



4 R: CH_3 **5** R: $C_6H_5CH_2$ **6** R: CH_3 R_2: $C_6H_5SO_2$ **7** R_1: CH_3 R_2: C_6H_5CO **8** R_1: $C_6H_5CH_2$ R_2: C_6H_5CO



9 R: CH_3 **10** R: $C_6H_5CH_2$ **11**

An examination of the deviations from the individual rings least- squares planes shows that, A(C5a, C5, C6, C7, C8, C8a), B(C4a, C5a, C8a, N9, C9a) and G(C11, C12, C13, C14, C15, C16) are planar. The maximum distances to the least-squares planes being 0.017 (9), -0.050(7) and 0.041 (9) Å, respectively. The rings C(C1, C2, C3, C4, C4a, C9a) and H(S1', C1, S3', C4', C5') are not planar with maximum deviations of C2 [0.320 (8)] and S3' [-0.774 (3)] Å. They are also twisted with respect to each other. The dihedral angles between the least-squares planes are A-B = 2.6(5), A-C = 3.6(3), A-G = 102.6(4), A-H = 86.7(4), B-C = 6.1(4), B-G = 100.0(4), B-H = 85.9(6), C-G = 106.2(3), C-H = 88.5(6), G-H = 66.7(5)°. The sums of the angles about N1 and N9 atoms are 359.8(5)° and 360.0(5)° respectively, so the atoms attached to them lie in a plane with the corresponding values of the bond length and angles given in Tables 1 and 2, respectively.

Table 1

Bond Distances (Å) of Compound **6**

S10	-	O1	1.443(5)	C1	-	C9a	1.480(10)
S10	-	O2	1.443(6)	C4a	-	C9a	1.390(10)
S10	-	N1	1.608(6)	C4a	-	C5a	1.400(10)
S10	-	C11	1.781(9}	C5a	-	C8a	1.420(10)
S1'	-	C1	1.843(8)	C5a	-	C5	1.410(10)
S1'	-	C5'	1.770(10)	C8a	-	C8	1.380(10)
S3'	-	C1	1.826(8)	C7	-	C8	1.380(10)
S3'	-	C4'	1.760(10)	C6	-	C7	1.380(10)
O3	-	C2"	1.414(9)	C5	-	C6	1.380(10)
O3	-	C17	1.420(10)	C4'	-	C5'	1.390(20)
N9	-	C9a	1.404(9)	C1"	-	C2"	1.500(10)
N9	-	C8a	1.390(10)	C11	-	C12	1.380(10)
N1	-	C4	1.479(8)	C12	-	C13	1.360(10)
N1	-	C1"	1.473(8)	C11	-	C16	1.390(10)
C4	-	C3	1.520(10)	C15	-	C16	1.390(10)
C4	-	C4a	1.510(10)	C14	-	C15	1.390(10)
C3	-	C2	1.530(10)	C13	-	C14	1.380(10)
C2	-	C1	1.540(10)				

The distance between S3'-H9 [2.941 (8) Å] shows the possibility of hydrogen bonding. The thermal parameters of C4' [1400] and C5' [1347 $Å^2$] are too high. The title molecule is highly strained which causes a distorted structure and unexpected bond lengths especially C4'-C5' [1.39 (2) Å] that is very small than the normal value.

There are attractions between O2-H4 [2.462 (10)], O1-H112' [2.545 (9)], O2-H12 [2.574 (11)] and O1-H16 [2.637 (12) Å] due to high electronegativity of oxygen atoms. These attractions cause molecular structure to be highly distorted. The increase in the thermal parameters of C1", C2", O3, C17 and atoms of the G ring (C13, C14, C15) may be also due to this highly strained structure.

The structure of 1,2,3,4-tetrahydrocarbazole-1-spiro-2'-(1,3)-dithiolane skeleton is widely affected by the existence of the substituent [$PhSO_2NC_2H_4OCH_3$] bonded at C4 position [14].

Table 2

Bond Angles (°) of Compound **6**

O2	-	S10	-	O1	119.8(4)	C4a	-	C9a	-	C1	127.7(7)
N1	-	S10	-	O1	106.7(3)	C9a	-	C4a	-	C4	120.9(7)
N1	-	S10	-	O2	108.5(3)	C5a	-	C4a	-	C4	130 8(8)
C11	-	S10	-	O1	108.5(3)	C5a	-	C4a	-	C9a	108.1(7)
C11	-	S10	-	O2	106.3(4)	C8a	-	C5a	-	C4a	107.6(7)
C11	-	S10	-	N1	106.4(4)	C5	-	C5a	-	C4a	136.3(8)
C5'	-	S1	-	C1	96.1(5)	C5	-	C5a	-	C8a	116.1(8)
C4'	-	S3'	-	C1	97.9(5)	C5a	-	C8a	-	N9	107.9(7)
C17	-	O3	-	C2"	111.7(6)	C8	-	C8a	-	N9	128.1(9)
C4	-	N1	-	S10	120.3(4)	C8	-	C8a	-	C5a	124.0(10)
C1"	-	N1	-	S10	121.6(5)	C7	-	C8	-	C8a	117.3(10)
C1"	-	N1	-	C4	117.9(5)	C6	-	C7	-	C8	121.4(9)
C8a	-	N9	-	C9a	108.1(6)	C5	-	C6	-	C7	120.9(10)
C3	-	C4	-	N1	112.5(7)	C6	-	C5	-	C5a	120.4(9)
C4a	-	C4	-	N1	110.6(6)	C4'	-	C5'	-	S1'	116.1(9)
C4a	-	C4	-	C3	110.4(6)	C5'	-	C4'	-	S3'	115.7(9)
C2	-	C3	-	C4	112.6(7)	C2"	-	C1"	-	N1	115.0(7)
C1	-	C2	-	C3	110.6(7)	C1"	-	C2"	-	O3	107.1(7)
S3'	-	C1	-	S1'	106.6(4)	C13	-	C12	-	C11	119.1(9)
C2	-	C1	-	S1'	111.4(5)	C12	-	C11	-	S10	120.7(7)
C2	-	C1	-	S3'	111.7(5)	C16	-	C11	-	S10	118.4(6)
C9a	-	C1	-	S1'	107.5(5)	C16	-	C11	-	C12	120.9(8)
C9a	-	C1	-	S3'	112.1(5)	C15	-	C16	-	C11	118.7(8)
C9a	-	C1	-	C2	107.5(7)	C14	-	C15	-	C16	120.5(9)
C1	-	C9a	-	N9	124.1(7)	C13	-	C14	-	C15	118.8(9)
C4a	-	C9a	-	N9	108.2(7)	C14	-	C13	-	C12	121.9(9)
H9	-	N9	-	C8a	126.0(5)	H9	-	N9	-	C9a	125.9(5)

EXPERIMENTAL

The ^{1}H-nmr spectra were obtained on a W Gemini-Varian 200 and Bruker WH-270 NMR spectrometer with tetramethylsilane as an internal standard. Infrared spectra were recorded on Hitachi 270-30 spectrometer. Melting points were measured on digital melting point apparatus (Gallenkamp) and are uncorrected. Analytical and preparative thin-layer chromatography was done on silica gel 60 HF-254 (Merck). Column chromatography was carried out by using 70-230 mesh silica gel (0.063-0.2 mm, Merck).

N-(2-Methoxyethyl)-*N*-{2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2-(1,3)dithiolane]-4-yl}benzenesulfonamide (**6**).

To a solution of 3.34 g (10 mmoles) of amine **4** and 2 ml of triethylamine in 30 ml of chloroform is added 2 ml of benzenesulfonyl chloride. The mixture is stirred for 1 hour at room temperature. After washing with 20 ml of 10% aqueous potassium carbonate, the organic layer is dried with magnesium sulfate and the solvent is evaporated. The residue is purified by chromatography using silica gel (ethyl acetate-benzene 1:1) to afford 4.08 g (86%) of **6** which was recrystallized from ethyl acetate, mp 217-218°; ir (potassium bromide): ν 3320 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.09-2.21 (m, 2H), 2.36-2.46 (m, 2H), 3.08-3.60 (m, 11H), 5.30-5.36 (dd, 1H, J = 6.67 and J = 7.66 Hz), 6.86-8.03 (m, 9H, aromatic protons), 8.40 (s, 1H, NH).

Anal. Calcd. for $C_{23}H_{26}N_2O_3S_3$ (474.65): C, 58.20; H, 5.52; N, 5.90. Found: C, 58.16; H, 5.59; N, 5.94.

N-Benzoyl-*N*-(2-methoxyethyl){2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'-(1,3)dithiolane]-4-yl}amine (**7**).

A solution of 3.34 g (10 mmoles) of amine **4** and 2 ml of triethylamine are dissolved in 25 ml of chloroform and 2 ml of benzoyl chloride added. The mixture is stirred for 2 hours at room temperature. Then extraction with 20 ml of 10% aqueous potassium carbonate follows. The organic layer is dried with magnesium sulfate and evaporated under reduced pressure. Purification of the residue by chromatography using silica gel and ethyl acetate yields 4.12 g (94%) of **7**, mp 202-203°; ir (potassium bromide): ν 3246 (NH), 1620 (amide) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.11-2.52 (m, 4H), 2.98-3.09 (m, 2H), 3.32 (s, 3H, OCH_3), 3.37-3.64 (m, 4H), 3.71-3.84 (m, 2H), 5.13-5.19 (dd, 1H, J = 5.55 and J = 8.80 Hz), 7.12-7.58 (m, 9H, aromatic protons), 8.36 (s, 1H, NH).

Anal. Calcd. for $C_{24}H_{26}N_2O_2S_2$ (438.60): C, 65.72; H, 5.97; N, 6.38. Found: C, 65.79; H, 5.96; N, 6.45.

N-Benzoyl-*N*-(2-benzyloxyethyl){2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'-(1,3)dithiolane]-4-yl}amine (**8**).

A solution of 2.75 g (10 mmoles) of **1**, 1.8 g (11 mmoles) of ferric chloride and 2 ml of benzyloxyethylamine in 60 ml of benzene are heated for 12 hours using a Dean Stark trap. Then the solvent is removed under reduced pressure, the residue is dissolved in ethanol/tetrahydrofuran (1:1) and cooled in an ice bath. With stirring 2 g (56 mmoles) of sodium borohydride are added in several portions. The ice bath is removed and the mixture is stirred for 7 hours under a nitrogen atmosphere. The solvent is evaporated under reduced pressure and the residue is dissolved in ethyl acetate. After washing with 10% aqueous sodium hydroxide the organic layer is dried with magnesium sulfate and the solvent is evaporated. The residue is dissolved in 50 ml of chloroform, 3 ml (21 mmoles) triethylamine and 3 ml (26 mmoles) of benzoyl chloride are added. The mixture is allowed

to stir for 30 minutes at room temperature. Then extraction with 10% sodium hydroxide follows. The organic layer is dried with magnesium sulfate and evaporated under reduced pressure. The residue is chromatographed using silica gel and chloroform-ethyl acetate (1:4). After evaporation of the solvent 2.6 g (50%) of the pure product is isolated, mp 157-158°; ir (potassium bromide): ν 3240 (NH), 1615 (amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.13-2.54 (m, 4H), 3.08-3.94 (m, 8H), 4.47-4.61 (dd, 2H, J = 12.09 and J = 15.4 Hz), 5.14-5.21 (dd, 1H, J = 5.46 and J = 8.88 Hz), 7.08-7.58 (m, 14H, aromatic protons), 8.53 (s, 1H, NH).

Anal. Calcd. for $C_{30}H_{30}N_2O_2S_2$ (514.69): C, 70.00; H, 5.87; N, 5.44. Found: C, 69.96; H, 5.92; N, 5.41.

4-[Benzoyl-(2-methoxyethyl)amine]-2,3,4,9-tetrahydro-1*H*-carbozol-1-one (**9**).

A solution of 3.2 g (7 mmoles) of the thioketal **7** and 3.0 g (8.33 mmoles) of benzeneseleninic anhydride are dissolved in 50 ml of anhydrous chloroform, 2 ml of pyridine is added. The mixture is stirred for 60 hours under a nitrogen atmosphere at room temperature. After washing with 30 ml of 10% aqueous sodium hydroxide the organic layer is dried with magnesium sulfate and solvent evaporated. The residue is chromatographed (silica gel-ethyl acetate) 1.8 g (70%) of the product is isolated, which is crystallized from diethyl ether, mp 214°, ir (potassium bromide): ν 3240 (NH), 1667 (Ketone) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.36-2.80 (m, 4H), 2.95-3.03 (m, 1H), 3.32 (s, 3H, OCH_3), 3.63-3.75 (m, 2H), 3.98-4.04 (m, 1H), 5.45 (t, 1H, J = 4.8 Hz), 7.18-7.65 (m, 9H, aromatic protons), 9.30 (s, 1H, NH).

Anal. Calcd. for $C_{22}H_{22}N_2O_3$ (362.42): C, 72.90; H, 6.11; N, 7.72. Found: C, 72.84; H, 6.15; N, 7.76.

4-[Benzoyl(2-benzyloxyethyl)amino]-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**10**).

To a solution of 2.57 g (5 mmoles) **8**, 2 g (5.6 mmoles) of benzeneseleninic anhydride in 60 ml of chloroform is added 2 ml of pyridine. The mixture is stirred for 48 hours under a nitrogen atmosphere at room temperature. Then extraction with 10% sodium hydroxide follows. The organic layer is dried with magnesium sulfate and evaporated. The residue is chromatographed using silica gel and ethyl acetate to afford 1.2 g, which is crystallized from diethyl ether, mp 172-173°, ir (potassium bromide): ν 3230 (NH), 1670 (ketone), 1615 (amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.34-2.80 (m, 4H), 3.02-3.12 (m, 1H), 3.70-3.93 (m, 2H), 4.05-4.13 (m, 1H), 4.52 (t, 2H, J = 9.56 Hz), 5.44 (t, 1H, J = 7.31 Hz), 7.20-7.79 (m, 14H, aromatic protons), 10.15 (s, 1H, NH).

Anal. Calcd. for $C_{28}H_{26}N_2O_3$ (438.52): C, 76.69; H, 5.97; N, 6.38. Found: C, 76.73; H, 5.99; N, 6.42.

4-[Benzoyl(2-hydroxyethyl)amino]-2,3,4,9-tetrahydrocarbazol-1-one (**11**).

To a solution of 2.2 g (5 mmoles) of **10** in tetrahydrofuran is added 200 mg of 20% palladium hydroxide (Pearlman's catalyst). The mixture is hydrogenated at room temperature for 40 hours. The catalyst is removed by filtration and the solution is evaporated. The residue is purified by chromatography using silica gel ethyl acetate to afford 1.12 g (64%) of **6**, mp 207° ir (potassium bromide): ν 3450 (OH), 3230 (NH), 1675 (ketone), 1620 (amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.21-2.23 (m, 2H), 2.14-2.45 (m, 1H), 2.70-2.75 (m, 1H), 3.34-3.74 (m, 4H), 4.72 (t, 1H, J = 5.5 Hz, OH), 5.00 (t, 1H, J = 7.0 Hz), 7.00-7.55 (m, 9H, aromatic protons) 11.10 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{20}N_2O_3$ (348.39): C, 72.39; H, 5.78; N, 8.04. Found: C, 72.42; H, 5.74; N, 8.08.

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