A Novel Synthesis of 6,7,8,9-Tetrahydro-5*H*-dibenzo[*c*,*g*]carbazole

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The synthesis of the title compound from 2-tetralone and thiosemicarbazide is reported. The structure was obtained by X-ray crystallography and its evaluation in certain anticonvulsant, cytotoxic and DNA binding screens is described.

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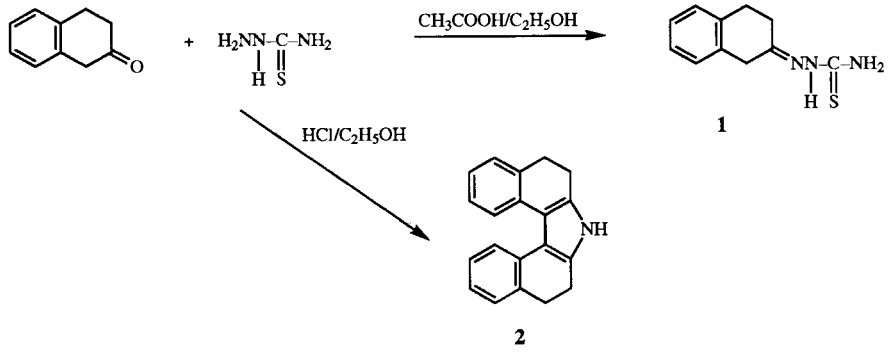
During the last few years, several papers from these laboratories have described the anticonvulsant[1-3] and anticancer [3] properties of thiosemicarbazones. In an attempt to prepare the thiosemicarbazone of 2-tetralone, namely compound **1**, reaction of this ketone with thiosemicarbazide in the presence of hydrochloric acid did not produce the desired compound. X-ray analysis of the product revealed it to be 6,7,8,9-tetrahydro-5*H*-dibenzo[*c*,*g*]carbazole **2**. The purpose of this report is to indicate a novel synthetic route to **2** and also to describe its structure revealed by X-ray crystallography as well as some biological evaluations of this compound.

Scheme 1



1

2

A review of the literature indicated that the synthesis of compound **2** has been described previously [4] by the Fischer indole synthesis. In this case, 2-tetralone was reacted with hydrazine in the presence of hydrochloric acid to produce **2** in good yield. An azine was postulated as an intermediate product in the reaction. In the present case, reaction of 2-tetralone with thiosemicarbazide to yield **2** probably involved the formation of **1** as a reaction intermediate. In order to test this hypothesis, compound **1** was heated in the presence of hydrochloric acid with and also without 2-tetralone; in both cases the dibenzocarbazole **2** was formed. Hence 2-tetralone thiosemicarbazone could react with either another molecule of **1** or alternatively 2-tetralone to form intermediates which would undergo intramolecular cyclization and subsequent rearrangement by a process analogous to the Fischer indole synthesis [5]. Presumably substituted 2-tetralones would give rise to analogs of **2** and hence the observation recorded in this study likely reveals a new general procedure for the synthesis of 6,7,8,9-tetrahydro-5*H*-diaryl[*c*,*g*]carbazoles.

The structure of **2** was confirmed by X-ray crystallography. Figure 1 is an ORTEP diagram of the molecule revealing a number of features of interest particularly its lack of planarity which is due, *inter alia*, to the following reasons. First, there is steric repulsion in the region of the atoms at positions 9 and 19 which is reflected in the bond lengths. The distances between the H9 and H19, H9 and C19, and H19 and C9 atoms are 2.39(2), 2.783(15) and 2.780(15)Å respectively, which are very close to the sums of the van der Waal radii for these pairs of interacting atoms. Figure 2 is a PLUTON CPK drawing [6] of compound **2** which illustrates these effects. Second, the sp^3 hybridization of the carbon atoms at positions 3, 4, 13 and

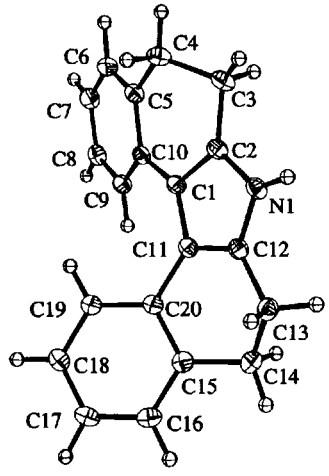


Figure 1. ORTEP drawing of compound **2**. The non-H atoms are represented with thermal ellipsoids drawn at the 50% probability level. For clarity the H atoms are drawn as small spheres of arbitrary size.

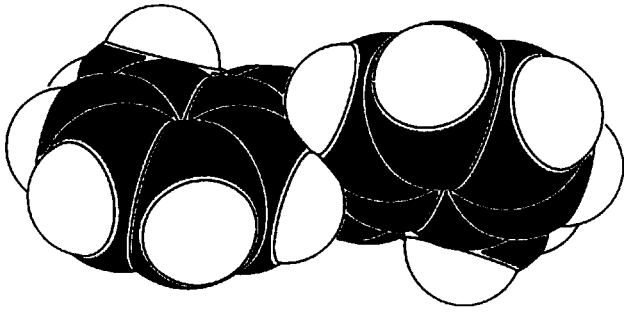


Figure 2. Edge on PLUTON CPK drawing of compound **2** showing the collision of the two aryl rings at the 9 and 19 positions

14 in the partially hydrogenated rings induces significant ring strain which would distort the molecule from planarity. The four sp^3 carbon atoms are puckered above and below the plane of the twisted molecule. These phenomena contribute to the observation that the angle between the two aryl rings is 50.137(47). The two aryl rings are planar within 0.0084(17)Å while the pyrrole nucleus is planar within 0.0100(17)Å. The molecule must twist into either of two mirror image conformations and the mirror image molecules are both found in the centrosymmetric crystal structure.

Table 1 indicates the bond distances in compound **2** while Table 2 reveals the torsion angles found in this molecule. In the case of the aryl rings, the carbon-carbon bond lengths were all in the range 1.385-1.41Å, which is normal for aromatic rings. The C1-C11 bond length in the heterocyclic ring is 1.437(2)Å, which is longer than the other four bonds in this ring, namely the range 1.365-1.378(2)Å. The bonds connecting the aryl and heterocyclic rings (C1-C10 and C11-C20) are intermediate in length between single and aromatic bonds, *viz* 1.466-1.473(2)Å. While the bonds between the sp^3 carbon atoms

Table 1

Bond Distances (Å) and Bond Angles (°) for 6,7,8,9-Tetrahydro-5*H*-dibenzo[*c*,*g*]carbazole at 123 K

N1-C2	1.3715(15)	C9-C10	1.3961(17)
N1-C12	1.3648(17)	C9-H9	0.992(15)
N1-H1N	0.882(16)	C11-C12	1.3775(16)
C1-C2	1.3761(17)	C11-C20	1.4657(17)
C1-C10	1.4729(15)	C12-C13	1.4893(17)
C1-C11	1.4374(17)	C13-C14	1.5353(19)
C2-C3	1.4860(18)	C13-H13A	1.010(15)
C3-C4	1.5341(18)	C13-H13B	0.995(14)
C3-H3A	1.007(14)	C14-C15	1.5126(17)
C3-H3B	1.000(14)	C14-H14A	1.029(15)
C4-C5	1.5129(18)	C14-H14B	0.993(14)
C4-H4A	1.002(15)	C15-C16	1.3901(19)
C4-H4B	1.039(16)	C15-C20	1.4103(17)
C5-C6	1.3952(17)	C16-C17	1.3967(18)
C5-C10	1.4070(18)	C16-H16	0.980(15)
C6-C7	1.3871(19)	C17-C18	1.3853(18)
C6-H6	1.028(16)	C17-H17	0.983(16)
C7-C8	1.3846(19)	C18-C19	1.3898(18)
C7-H7	1.016(15)	C18-H18	0.973(16)
C8-C9	1.3931(16)	C19-C20	1.3992(16)
C8-H8	0.995(15)	C19-H19	0.993(13)
C2-N1-C12	109.20(10)	C5-C10-C9	119.16(10)
C2-N1-H1N	126.6(11)	C1-C11-C12	106.47(11)
C12-N1-H1N	124.0(11)	C1-C11-C20	133.93(10)
C2-C1-C10	117.83(11)	C12-C11-C20	118.05(10)
C2-C1-C11	106.99(10)	N1-C12-C11	108.89(10)
C10-C1-C11	134.23(11)	N1-C12-C13	126.10(10)
N1-C2-C1	108.42(11)	C11-C12-C13	124.93(11)
N1-C2-C3	126.41(11)	C12-C13-C14	107.60(10)
C1-C2-C3	124.99(10)	C12-C13-H13A	110.4(9)
C2-C3-C4	107.42(10)	C12-C13-H13B	111.7(8)
C2-C3-H3A	110.5(9)	C14-C13-H13A	110.4(9)
C2-C3-H3B	111.8(8)	C14-C13-H13B	109.5(9)
C4-C3-H3A	110.7(8)	H13A-C13-H13B	107.3(11)
C4-C3-H3B	110.8(8)	C13-C14-C15	111.87(10)
H3A-C3-H3B	105.7(12)	C13-C14-H14A	108.5(9)
C3-C4-C5	111.43(10)	C13-C14-H14B	110.3(8)
C3-C4-H4A	110.4(8)	C15-C14-H14A	108.8(8)
C3-C4-H4B	108.6(8)	C15-C14-H14B	111.9(8)
C5-C4-H4A	111.4(8)	H14A-C14-H14B	105.2(11)
C5-C4-H4B	106.8(9)	C14-C15-C16	121.68(11)
H4A-C4-H4B	107.9(12)	C14-C15-C20	118.87(11)
C4-C5-C6	121.21(11)	C16-C15-C20	119.46(11)
C4-C5-C10	119.48(10)	C15-C16-C17	121.20(11)
C6-C5-C10	119.30(11)	C15-C16-H16	120.1(9)
C5-C6-C7	120.94(12)	C17-C16-H16	118.7(9)
C5-C6-H6	117.2(8)	C16-C17-C18	119.31(12)
C7-C6-H6	121.8(8)	C16-C17-H17	118.7(8)
C6-C7-C8	119.93(11)	C18-C17-H17	122.0(8)
C6-C7-H7	120.2(9)	C17-C18-C19	120.20(11)
C8-C7-H7	119.8(9)	C17-C18-H18	119.5(10)
C7-C8-C9	119.85(12)	C19-C18-H18	120.3(10)
C7-C8-H8	121.1(8)	C18-C19-C20	121.01(11)
C9-C8-H8	119.0(8)	C18-C19-H19	118.8(8)
C8-C9-C10	120.81(12)	C20-C19-H19	120.2(8)
C8-C9-H9	119.6(8)	C11-C20-C15	117.48(10)
C10-C9-H9	119.6(8)	C11-C20-C19	123.28(11)
C1-C10-C5	117.39(11)	C15-C20-C19	118.80(11)
C1-C10-C9	123.14(11)		

Table 2

Torsional Angles (°) for
6,7,8,9-Tetrahydro-5*H*-dibenzo[*c*,*g*]carbazole at 123 K

C12	N1	C2	C1	-0.8(1)	C12	N1	C2	C3	-176.0(2)
C2	N1	C12	C11	-0.5(1)	C2	N1	C12	C13	-177.2(2)
C10	C1	C2	N1	-168.8(2)	C10	C1	C2	C3	6.6(1)
C11	C1	C2	N1	1.7(1)	C11	C1	C2	C3	177.0(2)
C2	C1	C10	C5	-20.9(1)	C2	C1	C10	C9	152.6(2)
C11	C1	C10	C5	171.9(2)	C11	C1	C10	C9	-14.6(1)
C2	C1	C11	C12	-2.0(1)	C2	C1	C11	C20	163.0(2)
C10	C1	C11	C12	166.2(2)	C10	C1	C11	C20	-28.8(1)
N1	C2	C3	C4	-156.2(2)	C1	C2	C3	C4	29.3(1)
C2	C3	C4	C5	-49.9(1)	C3	C4	C5	C6	-138.5(2)
C3	C4	C5	C10	40.5(1)	C4	C5	C6	C7	178.4(2)
C10	C5	C6	C7	-0.6(1)	C4	C5	C10	C1	-3.7(1)
C4	C5	C10	C9	-177.5(2)	C6	C5	C10	C1	175.3(2)
C6	C5	C10	C9	1.5(1)	C5	C6	C7	C8	-0.8(1)
C6	C7	C8	C9	1.3(1)	C7	C8	C9	C10	-0.4(1)
C8	C9	C10	C1	-174.4(2)	C8	C9	C10	C5	-1.0(1)
C1	C11	C12	N1	1.5(1)	C1	C11	C12	C13	178.2(2)
C20	C11	C12	N1	-166.3(2)	C20	C11	C12	C13	10.5(1)
C1	C11	C20	C15	174.5(2)	C1	C11	C20	C19	-13.2(1)
C12	C11	C20	C15	-21.9(1)	C12	C11	C20	C19	150.4(2)
N1	C12	C13	C14	-158.5(2)	C11	C12	C13	C14	25.3(1)
C12	C13	C14	C15	-48.9(1)	C16	C15	C20	C11	174.2(2)
C16	C15	C20	C19	1.6(1)	C15	C16	C17	C18	0.6(1)
C16	C17	C18	C19	0.0(1)	C17	C18	C19	C20	0.2(1)
C18	C19	C20	C11	-173.2(2)	C18	C19	C20	C15	-0.9(1)

(C3-C4 and C13-C14) are in the normal range for saturated carbon atoms, the bonds from the C3, C4, C13 and C14 atoms to aromatic carbon atoms are somewhat shorter in length, namely 1.486-1.513(2)Å.

The interest in discovering prototypic anticonvulsant and antineoplastic agents in this laboratory suggested the bioevaluation of **2**. Utilization of established procedures which detect some anticonvulsant agents and neurotoxicity [7] revealed that this compound lacked anticonvulsant activity in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screens and did not display neurotoxicity when doses up to and including 300 mg/kg were given by the intraperitoneal route to mice. The effect of oral administration of compound **2** to rats (50 mg/kg) was observed in the MES and neurotoxicity screens over the time period of 0.25-4 hours. While no neurotoxicity was displayed, only marginal protection was noted in the MES screen whereby one of four rats was protected at the end of 2 and 4 hours. Compound **2** showed weak activity against P388-D1 lymphocytic leukemia cells having an IC_{50} figure of 18.3 μM. Recently the National Cancer Institute has introduced an *in vitro* screen whereby compounds are evaluated against approximately 60 human tumors from nine different neoplastic diseases [8]. One of the aims of this work is to detect compounds with preferential toxicity towards one or more groups of tumors. Leukemia cells were more sensitive to the effects of **2** than tumors in the other eight types of cancer and hence it is a useful lead antileukemic agent. A number of DNA binders contain fused ring systems [9]. Compound **2** was examined for its ability to bind to a synthetic deoxyribonucleic acid (DNA) namely poly[d(TG)]•poly[d(CA)] at *p*H 5 and 8 using concentrations up to 50 μg/ml. No increase in the melting temperature of the DNA was observed and the absence of binding may have been due, at least in part, to the lack of planarity of the molecule as revealed by X-ray crystallography.

In summary, a novel synthesis, X-ray crystallographic structure determination and some biological properties of 6,7,8,9-tetrahydro-5*H*-dibenzo[*c*,*g*]carbazole **2** are reported herein.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained using potassium bromide discs and a Beckman Aculab spectrophotometer. The letters m and s indicate medium and strong absorptions respectively. The ^{1}H nmr spectrum of **1** was determined on a Bruker AM 300 FT NMR instrument. The letters t, q, m, s and br are abbreviations for the words triplet, quartet, multiplet, singlet and broad respectively. Elemental analyses were performed using a Perkin-Elmer Model 2400 CHN Elemental Analyzer.

2-Tetralone Thiosemicarbazone (**1**).

A slurry of 2-tetralone (2.45 g, 0.016 mole), thiosemicarbazide (1.50 g, 0.016 mole) and acetic acid (2-3 drops) in ethanol (95%, 50 ml) was stirred at room temperature for 0.5 hour. The resultant precipitate was collected and recrystallized

from ethanol to give 2-tetralone thiosemicarbazone (**1**), mp 154° in 65% yield; ^{1}H nmr (deuteriochloroform): δ 2.50-2.55 (t) and 2.60-2.65 (q) 2H of 4-CH_2, 2.90-2.98 (2H, m, 3-CH_2), 3.58 (1H, s) and 3.64 (1H, s) 2H of 1-CH_2, 6.27 (1H, br s, NH), 7.16-7.26 (4H, m, aryl H), 8.46 (0.55H, br s, NH), 8.65 (0.45H, br s, NH); ir (potassium bromide): 3460 (m, NH), 3330 (m, NH), 3180 (w, NH), 1600 (s, C=C), 1520 (s, C=C), 860 (m), 775 (m, CH).

Anal. Calcd. for $C_{11}H_{13}N_3S$: C, 60.24; H, 5.97; N, 19.16. Found: C, 60.19; H, 6.15; N, 19.36.

Formation of 6,7,8,9-Tetrahydro-5*H*-dibenzo[*c*,*g*]carbazole (**2**) from 2-Tetralone.

A solution of 2-tetralone (2.45 g, 0.016 mole), thiosemicarbazide (1.50 g, 0.016 mole), hydrochloric acid (2 ml) and ethanol (95%, 50 ml) was heated under reflux for 24 hours. On cooling, the mixture was concentrated from which a solid (1.26 g) was obtained. Recrystallization of the precipitate from ethanol gave 6,7,8,9-tetrahydro-5*H*-dibenzo[*c*,*g*]carbazole (**2**), mp 248-250° (lit [4], mp 249-250°) in 24% yield.

Anal. Calcd. for $C_{20}H_{17}N$: C, 88.52; H, 6.32; N, 5.16. Found: C, 88.31; H, 6.33; N. 5.15.

Formation of 6,7,8,9-Tetrahydro-5*H*-dibenzo[*c*,*g*]carbazole (**2**) from 2-Tetralone Thiosemicarbazone.

A solution of 2-tetralone thiosemicarbazone (1.05 g, 0.0047 mole), 2-tetralone (0.73 g, 0.005 mole) and hydrochloric acid (2 ml) in ethanol (95%, 30 ml) was heated under reflux for 24 hours. On cooling, some of the solvent was removed giving rise to a precipitate (0.56 g, 43%) mp 234° which on recrystallization from ethanol gave compound **2**, mp 246-248° in 21% yield. This product and the compound prepared from 2-tetralone and thiosemicarbazide *vide supra* were identical as revealed by mixed melting point evidence and identical infrared spectra. The experiment was repeated except that 2-tetralone was omitted from the reaction mixture leading to the formation of **2**, mp 248-250° in 11% yield.

X-ray Analysis of **2**

The crystal system was triclinic with space group P1. Crystal dimensions were 0.30 x 0.13 x 0.10 mm. Data were collected at 123 K. The unit cell dimensions were a = 7.7819(13)Å, b = 8.2870(16)Å, c = 11.2224(19)Å, α = 71.448(16)°, β = 87.738(14)°, γ = 87.362(15)°, V = 685.15(21)Å^3 and Z = 2. Other relevant parameters were M_r = 271.36, D_x = 1.315 Mg m^{-3}, λ (CuKα) = 1.54056 Å. μ = 0.63 mm^{-1}, F(000) = 288.74. The cell parameters were obtained by least-squares analysis of 25 reflections with $20.20 < \theta < 38.32°$. An Enraf-Nonius CAD4 diffractometer was used for data collection and a total of 3814 reflections were collected with 2742 unique reflections while the number of reflections where $I > 2.5\sigma(I)$ was 2446. The index range was $-9 \le h \le 9$, $0 \le k \le 10$, $-12 \le l \le 13$, $[(\sin\theta)/\lambda]_{max}$ = 0.6309 Å^{-1}. The merging R value of the intensities was 0.013. No corrections were made for absorption. The structure was solved and refined using the NRCVAX program system [10]. All non-hydrogen atoms were found on an *E* map and were refined anisotropically. All hydrogen atoms were found in ΔF maps and were refined isotropically. The refinement used 38 atoms, 258 parameters and 2446 of the 2742 reflections to give final *R* value of 0.40, $wR = 0.049[w=1/\sigma^2(F_o) + 0.0001(F_o)^2]$ and S = 2.83. The atomic scattering factors were taken from the literature [11]. All calculations were performed on a 80486 personal computer. A list of the following parameters are available from the authors namely the (i) atomic parameters x, y, z and Biso (ii) anisotropic temperature factors and (iii) structure amplitude table.

Bioevaluation of Compound **2**

The anticonvulsant activity and neurotoxicity of **2** was undertaken using literature protocols [7]. Cytotoxicity testing using P388-D1 cells employed a published procedure [12] and evaluation of **2** against human tumors was undertaken by the National Cancer Institute [8]. Measurement of the extent of binding of **2** to poly[d(TG)]•poly[d(CA)] was carried out by a previously reported procedure [13] except that ethanol was used as the solvent.

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