Comparison of reactivities of 1- and 4-oxotetrahydrocarbazoles in reactions with nucleophilic and electrophilic reagents

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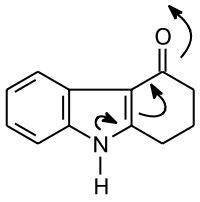
The half-wave potentials of polarographic reduction of the carbonyl group in unsubstituted and *N*-methyl- and *N*-phenylsulfonyl-substituted 1- and 4-oxotetrahydrocarbazoles and their reactivities in reactions with nucleophilic ($NaBH_4$, malonodinitrile, and cyanoacetamide) and electrophilic (DMF dimethyl acetal) reagents were compared. 4-Oxotetrahydrocarbazoles are much less reactive than 1-oxotetrahydrocarbazoles.

Key words: 1,2,3,9-tetrahydro-4*H*-carbazol-4-ones, 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones, reduction, voltammetry, dimethylformamide dimethyl acetal.

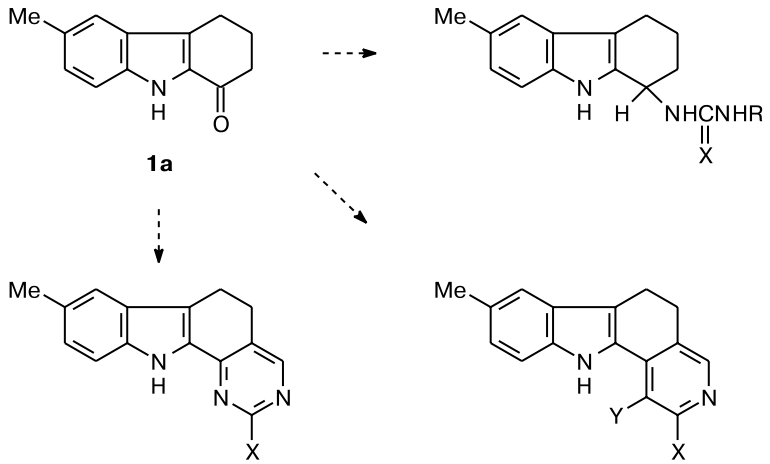
Fused carbazoles, for example, the antidepressants pyrazidole and tetrindole, belonging to the pyrazino[3,2,1-*j*,*k*]carbazole series are among important pharmaceuticals that are widely used in medical practice.[1—4] Recently, we have demonstrated that 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1a**) is a promising starting compound. In addition to the synthesis of pyrazinocarbazole derivatives based on **1a**, the latter can be used in two new approaches. Thus, compound **1a** can be involved in the synthesis of hydrogenated carbazoles containing the urea or thiourea substituents at position 1.[5] These compounds exhibited anticonvulsant activity in pharmacological experiments. Besides, compound **1a** can be used for the construction of tetracycles containing the fused pyridine or pyrimidine rings at positions 1 and 2 (Scheme 1).[6]



2a

The aim of the present study was to compare the reactivities of carbazolone **1a** and its analog, *viz.*, 1,2,3,9-tetrahydro-4*H*-carbazol-4-one (**2a**)[7] containing the oxo group at position 4. We expected that the

Scheme 1



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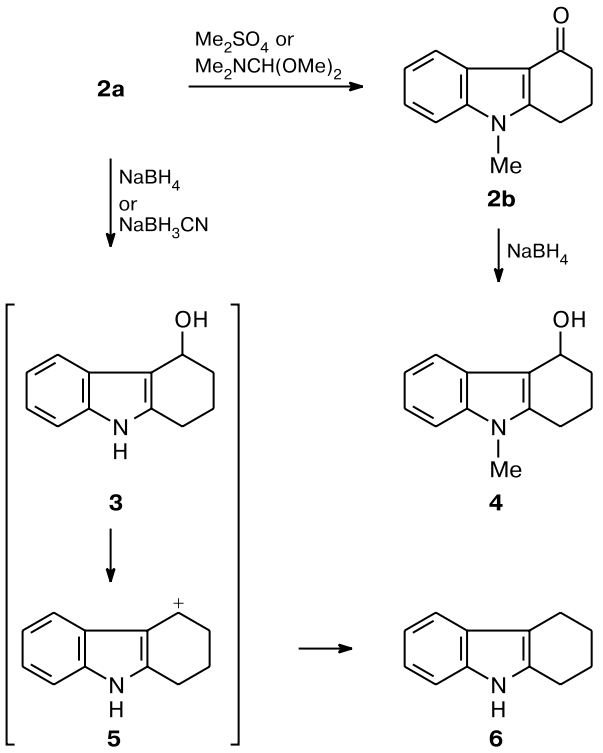
electron-withdrawing effect of the keto group on the adjacent CH_2 group in compound **2a** would be lower than that in 1-oxo derivative **1a**.

Actually, in some cases, compounds **1a** and **2a** differ substantially in the reactivity. For example, the reaction of **1a** with DMF dimethyl acetal afforded the 2-dimethylaminomethylene derivative, which was then transformed into pyridocarbazoles,[6] whereas condensation of **2a** with DMF dimethyl acetal under the same conditions involves only methylation of the indole nitrogen atom to form derivative **2b**. The latter was also prepared independently by methylation of **2a** with dimethyl sulfate (Scheme 2).

Scheme 2



Attempts to perform the reaction of ketone **2b** with DMF acetal under the same or even more drastic conditions (in an excess of acetal, 125 °C, 3 h or refluxing in an excess of acetal in DMF for 7 h) failed. In all cases, only the starting compound **2b** was isolated in high yield. An analogous situation was observed when attempting to perform condensation of ketone **2a** at the carbonyl group with such strong CH-acids as malonodinitrile and cyanoacetamide. These reactions with 1-oxo derivative **1a** occur rather easily[6] (ammonium acetate, AcOH in toluene, 60 °C, 5 h), whereas ketone **2a** does not react with these compounds under the same or even more drastic conditions (in the presence of MeONa in methanol or DMF on refluxing).

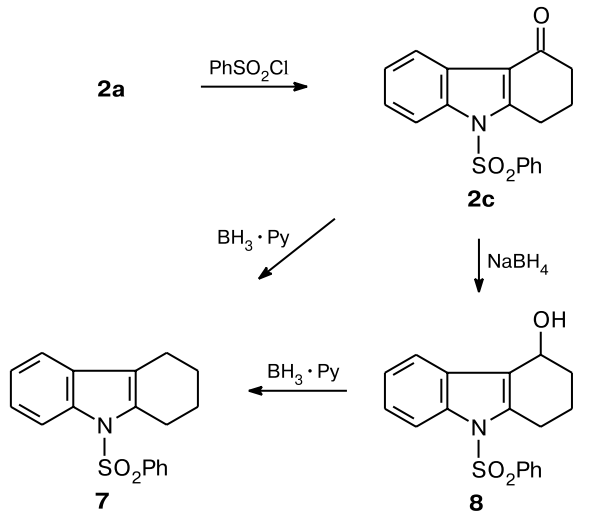
We also studied reduction of the oxo group in molecules **2a,b** and *N*-phenylsulfonyl derivative **2c** (which was prepared according to a procedure described earlier[8]), because it is the corresponding carbinols (reduction products) in the series of 1-substituted carbazoles that are the key compounds in the synthesis of the abovementioned anticonvulsants.

Earlier,[5] it has been found that reduction of ketone **1a** with sodium borohydride in ethanol at 50—55 °C was completed within 40 min. Under the same conditions, reduction of ketone **2a** (see Scheme 2) required 17 h for completion (TLC control, the disappearance of the starting ketone in the reaction mixture). However, the latter reaction did not produce the target alcohol **3**. Apparently, the reaction proceeds through the formation of carbocation **5**, and tetrahydrocarbazole **6** was the only product isolated in high yield. The latter was also prepared by reduction of substrate **2a** with sodium cyanoborohydride.

It should be noted that sodium borohydride reduces the carbonyl group of ketone **2a** to the hydroxy group under milder conditions (methanol—water, 20 °C, 14 h) with satisfactory selectivity, which allowed us to isolate and characterize alcohol **3**.[9]

We also performed reduction of *N*-substituted ketones **2b,c**. It appeared that reduction of *N*-methyl-substituted compound **2b** occurred smoothly at 80 °C for 1.5 h to give the target alcohol **4** in 67% yield. The reaction with *N*-phenylsulfonyl-substituted compound **2c** as the starting reagent (Scheme 3) afforded the corresponding alcohol **8** in 54% yield. It should be noted that the conditions of the reaction **2b** → **4** are more rigid that those used for reduction of ketone **1a**, whereas the reaction **2c** → **8** proceeds analogously to that with **1a**, under much milder conditions.

Scheme 3



Reduction of substrate **2c** with the complex $BH_3 \cdot Py$ instead of $NaBH_4$ afforded tetrahydrocarbazole **7** in 32% yield. The latter was also prepared by reduction of alcohol **8** with this complex. Apparently, the alcohols are intermediates in the transformation of ketones **2a** and **2c** into products **6** and **7**, respectively.

Therefore, ketone **2a** differs substantially in the reactivity from ketone **1a**, and this difference can be associated with the fact that the carbonyl group in molecule **2a** is attached to electron-rich position 3 of the indole fragment.

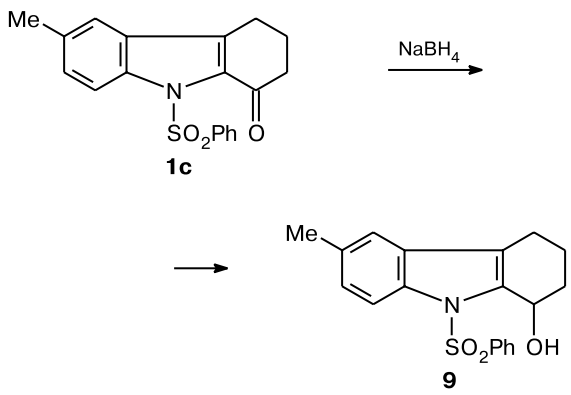
The qualitative characterization of the reactivities agrees well with the half-wave potentials ($E_{1/2}$) of polarographic reduction of ketones **1** and **2**.

Compound	**1a**	**1b**	**1c**	**2a**	**2b**	**2c**
$E_{1/2}$/V	−2.17	−2.16	−1.78	−2.73	−2.67	−1.83

The half-wave potentials $E_{1/2}$ characterizing polarographic reduction of ketones are known[10] to correlate with the ability of the substituents to change the electron density on the ketone carbonyl group. As can be seen from the polarographic data, our main assumption that the carbonyl group at position 4 of the carbazole ring possesses higher electron density than that at position 1 was completely confirmed. A comparison of the half-wave potentials of parent ketones **1a** and **2a** ($\Delta E_{1/2}$ = 0.56 eV) shows that the latter is more difficult to reduce. This is evidence that the carbonyl group in compound **2a** provides lower CH-acidity of the adjacent methylene group than the carbonyl group in compound **1a**, which is responsible for the fact that DMF acetal cannot undergo condensation at this position under the conditions used. At the same time, the low electrophilicity of the C=O group in compound **2a** prevents condensation at the carbon atom of compounds containing the active methylene group. The carbonyl group at position 4 accepts the electron upon polarographic reduction or the hydride ion upon reduction with sodium borohydride less readily (compared to position 1), which accounts for the above-described characteristic features of reduction (electrochemical reduction of ketone **2a** occurs with difficulty, whereas removal of the hydroxy group from reduced product **3** in the reaction with borohydride occurs easily). It should be noted that the introduction of a strong electron-withdrawing substituent at position 1 of the indole fragment gives rise to compounds **1c** and **2c** characterized by similar $E_{1/2}$, and reduction of these compounds with sodium borohydride affords the corresponding alcohols **8** (see Scheme 3) and **9** (Scheme 4) under the same conditions (see the Experimental section).

The comparative study of the properties of ketones of the tetrahydrocarbazole series showed that ketones containing the carbonyl group at position 4 (compounds **2a,b**) are less reactive in reactions with electrophilic and nucleophilic reagents than the corresponding isomers containing the carbonyl group at position 1 (compounds of type **1**). This difference is apparently attributed to a substantial increase in the electron density at position 4 compared to position 1.

Scheme 4



1c **9**

Experimental

The mass spectra were recorded on a JSQ-900 spectrometer using a direct inlet system. The ^{1}H NMR spectra were measured on a Bruker AC-200 spectrometer in DMSO-d_6.

Polarographic measurements were carried out on a PU-1 polarograph (Belarus). The half-wave potentials $E_{1/2}$ are given for the first reduction wave at a dropping mercury electrode relative to a saturated calomel electrode. The concentration of the compound under study was $2.3 \cdot 10^{-4}$ mol L^{-1} in a 0.01 *M* tributylammonium iodide solution in DMF.

The course of the reactions and the purity of the compounds were monitored by TLC on Silufol UV-254 plates using a 1 : 1 ethyl acetate—benzene system as the eluent. The microanalysis data and mass spectra of compounds **1c**, **2b**, **4**, and **7**—**9** are given in Table 1. The ^{1}H NMR spectroscopic data are presented in Table 2. 6,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1b**) has been prepared earlier.[11]

6-Methyl-9-phenylsulfonyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (1c). Sodium hydride (80% suspension, 0.39 g, 13 mmol) was added to a solution of ketone **1a** (2 g, 10 mmol) in THF (30 mL) under argon, and the mixture was stirred at room temperature for 1 h. Benzene sulfochloride (1.8 mL, 14 mmol) was added to the resulting yellow suspension for 10 min in such a way that the temperature was maintained below 25 °C. The reaction solution was stirred at room temperature for 3.5 h. The solvent was distilled off, the residue was diluted with water (70 mL), and the resulting precipitate was filtered off, washed with water, and dried *in vacuo*. After recrystallization from DMF, compound **1c** was obtained in a yield of 1 g (31%), m.p. 185—187 °C.

1,2,3,9-Tetrahydro-4*H*-carbazol-4-one (2a) was synthesized according to a known procedure[7] from cyclohexane-1,3-dione monophenylhydrazone[12] in 41% yield, m.p. 218—220 °C.

9-Methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (2b). ***A.*** A suspension of compound **2a** (0.46 g, 2.5 mmol) in DMF dimethyl acetal (3.3 mL) was refluxed with stirring for 3 h. The resulting solution was cooled to 15 °C. The precipitate that

Table 1. Elemental analysis and mass spectrometric data for substituted tetrahydrocarbazoles **1c**, **2b**, **4**, and **7—9**

Compound	Found / Calculated (%)				Molecular formula	MS, m/z (I_{rel} (%))
	C	H	N	S		
1c	67.34	5.09	4.07	9.45	$C_{19}H_{17}NO_3S$	339 $[M]^+$ (21), 198 $[M - SO_2Ph]^+$ (18),
	67.24	5.05	4.13	9.45		156 $[M - CH_2CO - SO_2Ph]^+$ (100)
2b	78.01	6.78	7.05	—	$C_{13}H_{13}NO$	199 $[M]^+$ (23)
	78.36	6.58	7.03			
4	77.63	7.60	6.84	—	$C_{13}H_{15}NO$	201 $[M]^+$ (17)
	77.58	7.51	6.96			
7	69.81	5.48	4.51	10.15	$C_{18}H_{17}NO_2S$	311 $[M]^+$ (58),
	69.43	5.50	4.50	10.30		170 $[M - SO_2Ph]^+$ (100)
8	66.09	5.01	4.12	10.02	$C_{18}H_{17}NO_3S$	327 $[M]^+$ (51), 310 $[M - OH]^+$ (10),
	66.03	5.23	4.28	9.79		186 $[M - SO_2Ph]^+$ (61), 168 $[M - OH - SO_2Ph]^+$ (100)
9	66.52	5.45	4.06	9.70	$C_{19}H_{19}NO_3S$	341 $[M]^+$ (36), 323 $[M - H_2O]^+$ (54),
	66.84	5.61	4.10	9.39		182 $[M - H_2O - SO_2Ph]^+$ (100)

Table 2. ^{1}H NMR spectra of substituted tetrahydrocarbazoles **1c**, **2b**, **4**, and **7—9**

Compound	δ (J/Hz)		
	H(1)—H(4)	H(5)—H(8)	Substituent at the N(9) atom
1c[a]	2.08 (q, 2 H, 2 H(3)); 2.54, 2.92 (both t, 2 H each, 2 H(2), 2 H(4), J = 6.0)	7.43 (dd, 1 H, H(7), J_o = 8.8, J_m = 1.7); 8.10 (d, 1 H, H(8), J_o = 8.8)	7.52—7.76 (m, 4 H)[b]; 8.01 (m, 2 H)
2b	2.19 (q, 2 H, 2 H(2)); 2.43, 3.00 (both t, 2 H each, 2 H(1), 2 H(3), J = 6.0)	7.18 (m, 2 H); 7.45, 8.01 (both m, 1 H each)	3.74 (s, 3 H, Me)
4	1.94, 2.37, 2.70 (all m, 3 H each, 1 H, 2 H, 2 H(1), 2 H(2), 2 H(3)); 5.01 (t, 1 H, J = 3.4)[c]	7.03 (m, 2 H); 7.32, 7.54 (both m, 1 H each)	3.58 (s, 3 H, Me)
7	1.79 (m, 4 H, 2 H(2), 2 H(3)); 2.55, 3.00 (both m, 2 H each, 2 H(1), 2 H(4))	7.26 (m, 2 H); 7.40 (m, 1 H); 7.60 (m, 3 H); 7.80 (m, 2 H); 8.02 (m, 1 H)	
8	1.81, 2.94 (both m, 4 H each, 2 H, 2 H(1), 2 H(2), 2 H(3)); 4.78 (m, 1 H, H(4))[c]	7.26 (m, 2 H); 7.63 (m, 4 H); 7.86 (m, 2 H); 8.01 (m, 1 H)	
9[a]	1.62—2.12 (m, 4 H)[d]; 4.99 (m, 1 H, H(1))[c]	7.13 (dd, 1 H, H(7), J_o = 8.8, J_m = 1.7); 7.24 (br.s, 1 H, H(5)); 7.85 (d, 1 H, H(8), J_o = 8.8)	7.42—7.70 (m, 3 H); 7.98 (m, 2 H)

[a] The spectra of **1c** and **9** show signals of C(6)Me at δ 2.43 (s, 3 H) and 2.34 (s, 3 H), respectively.
[b] The signal for H(5) falls in this region.
[c] In the spectrum of **4**, the signal for OH is absent due to exchange with water of the solvent; the spectra of **8** and **9** have the signal at δ 5.05 (d, 1 H, J = 6.6 Hz) and 5.25 (br.s, 1 H), respectively.
[d] Some of the 2 H(2)—2 H(4) signals are observed at δ 2.38—2.79 and overlap with the signal of the solvent (δ 2.50).

formed was filtered off, washed with MeOH (2 mL), dried *in vacuo*, and recrystallized from MeOH to obtain ketone **2b** in a yield of 0.32 g (65%), m.p. 196—197 °C (*cf.* lit. data[13]: m.p. 198—200 °C).

B. A solution of NaOH (12.8 g) in water (25 mL) was added to a solution of ketone **2a** (11.56 g, 62 mmol) in acetone (75 mL). Then dimethyl sulfate (13.3 mL) was added with vigorous stirring for 10 min. The reaction mixture warmed up to 45 °C and the alkylation product precipitated. The resulting suspension was stirred at room temperature for 1 h and diluted with water (100 mL). The precipitate was filtered off, washed with water, dried *in vacuo*, and recrystallized from benzene to give ketone **2b** in a yield of 10.35 g (83%), m.p. 196—197 °C.

9-Phenylsulfonyl-2,3,4,9-tetrahydro-1*H*-carbazol-4-one (2c) was synthesized from ketone **2a** and benzene sulfochloride according to a procedure described earlier,[8] the yield was 60%, m.p. 169—170 °C (*cf.* lit data[8]: m.p. 170 °C).

4-Hydroxy-9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (4). A mixture of ketone **2b** (1 g, 5 mmol), $NaBH_4$ (0.9 g, 24 mmol), and EtOH (20 mL) was refluxed with stirring for 1.5 h. The ethanol was distilled off and the reaction mixture was diluted with water (50 mL). The precipitate was filtered off, dried, and recrystallized from benzene. The yield of alcohol **4** was 0.67 g (67%), m.p. 159—162 °C (with decomp.).

2,3,4,9-Tetrahydro-1*H*-carbazole (6). ***A.*** Sodium borohydride (0.9 g, 24 mmol) was added to a suspension of ketone **2a**

(1 g, 5.4 mmol) in EtOH (20 mL). The reaction mixture was stirred at 45—50 °C for 17 h. The ethanol was distilled off and the paste-like residue was mixed with water (50 mL). The precipitate was filtered off, washed with water, dried *in vacuo*, and recrystallized from hexane to obtain compound **6** in a yield of 0.56 g (61%), m.p. 118—120 °C. (*cf.* lit data[14]: m.p. 114—116 °C).

B. A 11% HCl solution in MeOH was added to a suspension of ketone **2a** (0.5 g, 2.7 mmol) and $NaBH_3CN$ (0.18 g, 2.8 mmol) in MeOH (5 mL) to pH 3. The reaction mixture was stirred at room temperature for 20 h, filtered, neutralized with Na_2CO_3, and evaporated on a rotary evaporator. The residue was worked up as described above (method *A*). Compound **6** thus prepared was identical to that described above, the yield was 0.27 g (58%).

9-Phenylsulfonyl-2,3,4,9-tetrahydro-1*H*-carbazole (7). ***A.*** A 95% $BH_3 \cdot Py$ (0.8 mL, 7.5 mmol) was added portionwise to a suspension of ketone **2c** (1.0 g, 3 mmol) in MeOH (20 mL) cooled to −5 °C under argon, the temperature being maintained in the range from −5 to −2 °C. Then the reaction mixture was cooled to −10 °C, and a 11% HCl solution in MeOH (6.2 mL) was added in such a way that the temperature was maintained below −5 °C, and kept at room temperature for 3.5 h. The reaction mixture was neutralized with a solution of NaOH (0.6 g) in water (10 mL). The precipitate was filtered off, washed with water, dried *in vacuo*, and recrystallized from MeCN to obtain compound **7** in a yield of 0.3 g (32%), m.p. 106—108 °C (*cf.* lit. data[15]: m.p. 107—109 °C).

B. Compound **7** was synthesized according to the above-described procedure (method *A*) from carbinol **8** (0.5 g, 1.5 mmol) and 95% $BH_3 \cdot Py$ (0.34 mL, 3.7 mmol) in a yield of 0.32 g (69%), m.p. 106—108 °C.

4-Hydroxy-9-phenylsulfonyl-2,3,4,9-tetrahydro-1*H*-carbazole (8). Sodium borohydride (0.8 g, 21 mmol) was added to a suspension of ketone **2c** (*cf.* lit data[8]) (1.5 g, 4.6 mmol) in EtOH (20 mL) and the reaction mixture was stirred at room temperature for 7 h. The ethanol was distilled off on a rotary evaporator. Water (70 mL) was added to the paste-like residue. The precipitate was filtered off, washed with water, dried *in vacuo* over $CaCl_2$ at 50 °C, and recrystallized from Pr^iOH to obtain alcohol **8** in a yield of 0.81 g (54%), m.p. 146—150 °C.

1-Hydroxy-6-methyl-9-phenylsulfonyl-2,3,4,9-tetrahydro-1*H*-carbazole (9). Sodium borohydride (0.25 g, 6.6 mmol) was added to a suspension of ketone **1c** (0.50 g, 1.5 mmol) in EtOH (5 mL) and the reaction mixture was stirred at room temperature for 6 h. The ethanol was distilled off and the residue was treated with water (20 mL). The precipitate was filtered off, washed with water, dried *in vacuo*, and recrystallized (0.37 g from 3 mL of MeCN) to obtain alcohol **9** in a yield of 0.30 g (59%), m.p. 147—149 °C.

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