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Unexpected Redox Processes in the Reactions of 1-Bromo- and 1,2-Epoxy-9-(*p*-tolylsulfonyl)-1,2,3,4,4a,9a-hexahydrocarbazoles with Acetyl Bromide

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Abstract—1,2-Epoxy-9-(*p*-tolylsulfonyl)-1,2,3,4,4a,9a-hexahydrocarbazole reacted with acetyl bromide on heating to give 1-acetoxy-2-bromo-9-(*p*-tolylsulfonyl)-1,2,3,4,4a,9a-hexahydrocarbazole and 1-acetoxy-9-acetyl-2,6-dibromo-1,2,3,4,4a,9a-hexahydrocarbazole. The structure of the latter was proved by X-ray analysis. Analogous reaction of 1-bromo-9-(*p*-tolylsulfonyl)-1,2,3,4,4a,9a-hexahydrocarbazole with acetyl bromide led to the formation of 9-acetyl-1,6-dibromo-1,2,3,4,4a,9a-hexahydrocarbazole.

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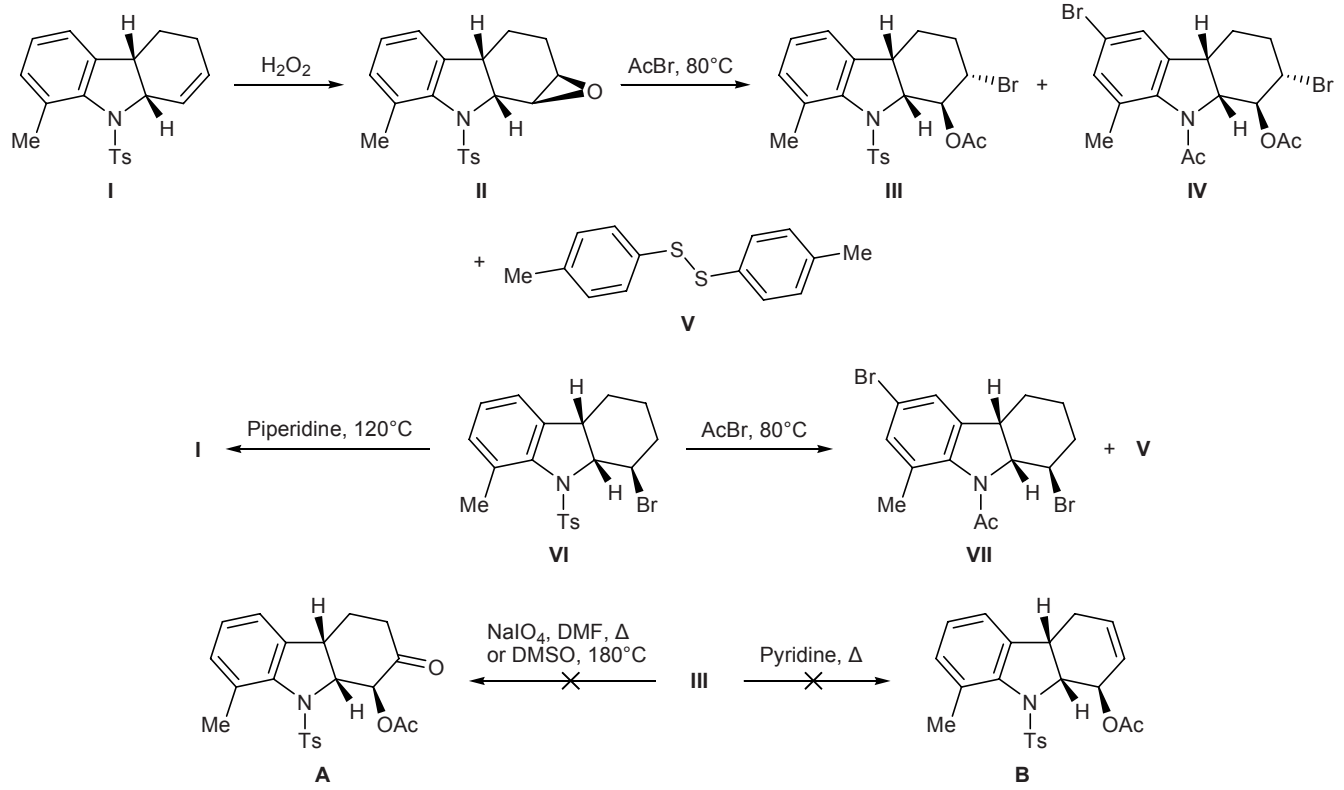
Some partially hydrogenated carbazoles have found application in the synthesis of biologically active compounds and hence attracted researchers' attention [1, 2]. Among such carbazole derivatives, those having functional groups in the cyclohexane ring are also important. They can be prepared via stereoselective halocyclization of *N*-alkyl- or *N*-arylsulfonyl-2-(cyclohex-2-en-1-yl)anilines, which gives 1-halohexahydrocarbazoles. The latter undergo dehydrohalogenation to the corresponding tetrahydro derivatives **I** on heating in piperidine [3].

The subsequent oxidation of tetrahydrocarbazole (**I**) with nitrogen(II) oxide [4] or dimethyldioxirane occurs with complete stereoselectivity and gives the only epoxy derivative **II** with *trans* orientation of the oxirane and pyrrole rings with respect to the cyclohexane ring. Presumably, in both cases the aromatic ring in molecule **I** hampers access to the double $C^1=C^2$ bond by oxidant due to axial orientation of the C^{4a}–C^{4b} bond; therefore, attack by oxidant is possible only at the side opposite to the nitrogen atom. As we found previously [4], stereochemistry of the oxirane ring opening is also controlled by the molecular structure.

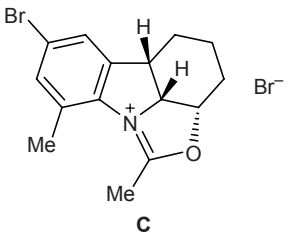
We made attempts to synthesize ketone **A** via oxidation of compound **III** at C^2 ($NaIO_4$, DMF, 160°C [5], or DMSO, 160°C [6, 7]) and tetrahydrocarbazole **B** via dehydrobromination of the same compound. For this purpose, we examined opening of the oxirane ring in epoxide **II** by the action of acetyl bromide on heating. When the reaction was carried out for ~4 h with protection from atmospheric moisture, the only product was acetate **III** whose R_f value was almost the same as that of the initial epoxide. The reaction performed without protection from atmospheric moisture gave 1-acetoxy-9-acetyl-2,6-dibromo derivative **IV** (Scheme 1). We tried to improve the yield of **IV** by adding several drops of water. In fact, the rate of formation of compound **IV** considerably rose, but the yield did not increase to an appreciable extent, presumably as a result of tarring due to increased concentration of HBr. It is known [6–8] that heating of some aralkyl halides in dimethyl sulfoxide leads to reduction of the latter to dimethyl sulfide. In the above reactions we isolated di-*p*-tolyl disulfide **V** which was formed via reduction of the *p*-tolylsulfonyl group with bromide ion. The latter was oxidized to Br^+ which replaced the 6-H proton in the aromatic ring of hexahydrocarbazole.

By reaction of 1-bromo-9-(*p*-tolylsulfonyl)hexahydrocarbazole (**VI**) [3] with acetyl bromide we obtained

Scheme 1.



9-acetyl-1,6-dibromohexahydrocarbazole **VII** and disulfide **V**. Elemental analysis of product **VII** showed the absence of anionic bromine; furthermore, good solubility of **VII** in chloroform and its spectral parameters suggest that the 2-bromine atom in molecule **VII** is more stable than iodine in analogous compound to intramolecular replacement by the oxygen atom of the acetyl fragment. Therefore, quaternary salt like **C** is not formed. However, the existence of equilibrium **V** ⇄ **VII** strongly displaced to the right cannot be ruled out completely [9].



C

Presumably, the axial bromine atom on C^2 in molecule **III** is stable to oxidation and elimination. Our attempts to oxidize compound **III** to ketone **A** with $NaIO_4$ in boiling DMF or with DMSO at 180°C were unsuccessful. Likewise, bromide **III** remained unchanged after prolonged heating in boiling pyridine.

The structure of the isolated compounds was determined on the basis of analytical and spectral data. The structure of disulfide **V** was consistent with its ^1H and ^{13}C NMR spectra. The electron-impact mass spectrum of **V** contained the molecular ion peak with *m*/*z* 246 and fragment ion peaks with *m*/*z* 123 $[CH_3C_6H_4S]^+$ (100%) and 92 $[CH_3C_6H_5]^+$. In the ^1H NMR spectrum of **IV** in $CDCl_3$, the 5-H and 7-H protons resonated as two one-proton singlets at δ 7.09 and 7.30 ppm, while signals from 1-H, 2-H, 4a-H, and 9a-H were poorly resolved. In the spectrum of **IV** recorded in acetone-d_6, signals from the aromatic 5-H and 7-H protons coincided (δ 7.15 ppm), and signals from 1-H, 2-H, 4a-H, and 9a-H were resolved well. The coupling constant for 1-H (δ 4.70 ppm) and 9a-H (δ 4.55 ppm) was about 8.0 Hz. The coupling constant between 1-H and 2-H (^3J = 12.0 Hz) indicated axial orientation of these protons. The 2-H proton (δ 4.07 ppm) showed two large couplings (J = 12.0 Hz) with the axial 1-H and 3a-H protons and one small coupling with the equatorial 3-H proton (J = 3.8 Hz). The 4a-H signal was a multiplet due to small couplings with protons on C^4 and probably long-range coupling with 3-H_{eq} (*W*-coupling).

The above orientations of protons in molecule **IV** was unambiguously proved by X-ray analysis (Fig. 1).

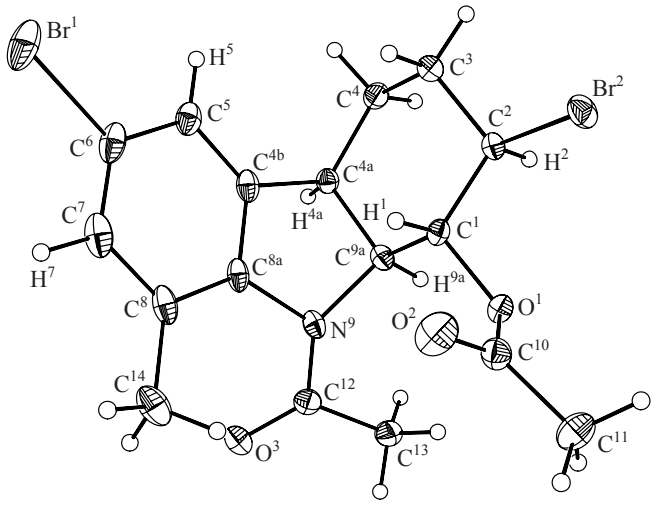


Fig. 1. Structure of the molecule of 9-acetyl-2,6-dibromo-8-methyl-1,2,3,4,4a,9a-hexahydrocarbazol-1-yl acetate (**IV**) according to the X-ray diffraction data; non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%; some hydrogen atoms are also shown.

The five-membered nitrogen-containing ring has an *envelope* conformation with the C^{9a} atom deviating by 0.565 Å from the plane formed by the four remaining atoms. The saturated six-membered ring adopts a *chair* conformation, and the substituents on C^1 and C^2 occupy equatorial positions, in keeping with the ^{1}H NMR data. Molecules **IV** in crystal give rise to chains along the *b* crystallographic axis via slightly shortened intermolecular contacts $Br^1 \cdots Br^{2c}$ (2 – *x*, –*y*, –*z*), 3.8696(5) Å, and shortened contacts $Br^1 \cdots Br^{2a}$ (*x*, *y* – 1, *z*), 3.6384(5) Å (Fig. 2). The other intermolecular

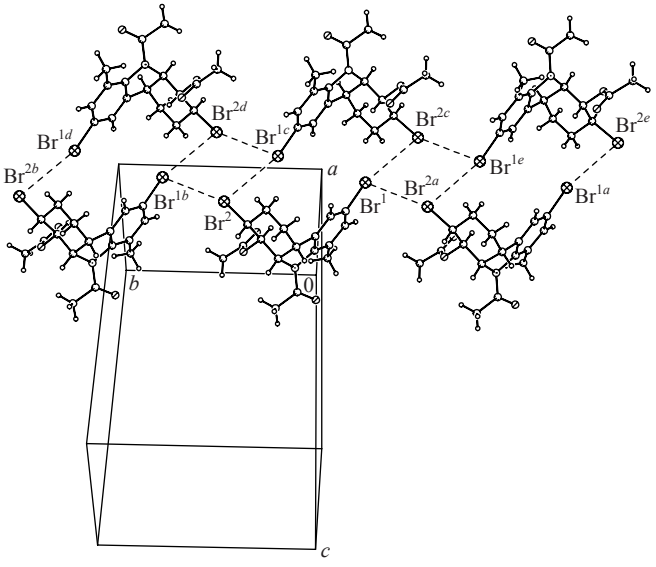


Fig. 2. A fragment of crystal packing of 9-acetyl-2,6-dibromo-8-methyl-1,2,3,4,4a,9a-hexahydrocarbazol-1-yl acetate (**IV**).

interactions conform to the corresponding van der Waals distances.

In the ^{13}C NMR spectra of **III** and **IV**, the C^2 signal is located at δ_C 48.9 and 49.3 ppm, respectively. An appreciably downfield position of the C^3 signal (δ_C 31.2 and 31.0 ppm, respectively) is related to α-effect of heavy bromine atom [10], whereas α-effect of the oxygen atom on C^2 in analogous compounds is much weaker [4]. The presence of two one-proton singlets in the aromatic region of the ^{1}H NMR spectrum of **VII**, δ 7.02 and 7.20 ppm (5-H, 7-H), indicates the presence of a substituent on C^6. The substituent on C^1 occupies equatorial position, as follows from two large coupling constants for 1-H (J = 13.2, 15.0 Hz; diaxial interaction) and small coupling with 2-H_{eq} (J = 4.4 Hz) [11].

Thus the reactions of 1-bromo- and 1,2-epoxy-9-(*p*-tolylsulfonyl)-1,2,3,4,4a,9a-hexahydrocarbazoles with acetyl bromide in the presence of moisture lead to introduction of bromine into the 6-position and are accompanied by replacement of the *p*-tolylsulfonyl group on the nitrogen by acetyl group. The *p*-tolylsulfonyl group acts as oxidant toward bromide ion and is reduced to di-*p*-tolyl disulfide.

EXPERIMENTAL

A single crystal of compound **IV** was obtained by slow crystallization from 95% ethanol. Monoclinic crystal system with the following unit cell parameters (100 K): a = 8.5214(6), b = 11.0319(7), c = 18.6968(12) Å; β = 90.6910(10)°; V = 1757.5(2) Å^3; Z = 4; d_{calc} = 1.682 g/cm^3; μ = 4.626 mm^{-1}; space group $P2_1/n$. Intensities of 22262 reflections were measured at 100 K on a Smart Apex2 CCD diffractometer [λ(MoK_α) = 0.71073 Å, graphite monochromator, 2θ < 60°]. The initial array of experimental reflection intensities was processed by SAINT and SADABS programs incorporated into APEX2 software [12] with account taken of correction for absorption (T_{min} = 0.474, T_{max} = 0.630). The structure was solved by the direct method and was refined with respect to F^2_{hkl} by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms. The positions of hydrogen atoms were set on the basis of geometry considerations and were refined using the riding model [U_{iso}(H) = nU_{eq}(C); n was assumed equal to 1.5 for methyl carbon atoms and to 1.2 for the other carbon atoms]. The final divergence factors were R_1 = 0.0395 [for 4175 reflections with $I > 2\sigma(I)$] and wR_2 = 0.0909 (for all 5108 independent reflections,

R_{int} = 0.0402); goodness of fit 0.984. All calculations were performed using SHELXTL-97 software [13].

The IR spectra were recorded on a UR-20 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-300 instrument at 300.13 and 75.47 MHz, respectively, using tetramethylsilane as internal reference. The elemental compositions were determined on an M-185B CHN analyzer. The mass spectra (electron impact, 70 eV) were obtained on an MKh-1320 instrument. Silica gel LS (40–100 μm, Lancaster) was used for column chromatography. Qualitative TLC analysis was performed on Sorbfil plates (*Sorbpolimer* Ltd., Krasnodar, Russia); spots were visualized by treatment with iodine vapor.

(1*S*,2*R*,4a*S*,9a*R*)-1,2-Epoxy-8-methyl-9-(*p*-tolylsulfonyl)-1,2,3,4,4a,9a-hexahydrocarbazole (II) was synthesized by oxidation of 0.034 g (0.1 mmol) of compound **I** with dimethyldioxirane according to the procedure described in [14]. After removal of the solvent, the residue was subjected to chromatography using a 1×15-cm column charged with 0.1 g of silica gel (eluent benzene). Yield 0.028 g (80%). The physical constants and spectral parameters of compound **II** were consistent with those reported in [4].

Reaction of compound II with acetyl bromide. Acetyl bromide, 15.5 mmol, was added to a solution of 0.55 g (1.55 mmol) of compound **II** in 20 ml of benzene. The mixture was heated for 70 h at 80°C, diluted with 150 ml of methylene chloride, and washed with a 10% aqueous solution of sodium hydrogen carbonate and with water. The organic phase was separated, dried over $MgSO_4$, and evaporated under reduced pressure, and the residue was subjected to chromatography on silica gel using benzene as eluent.

Di-*p*-tolyl disulfide (V). Yield 0.088 g (46%). ^{1}H NMR spectrum (CCl_4–C_6D_6), δ, ppm: 2.22 s (CH_3), 6.94 d and 7.28 d (4H each, H_{arom}, J = 8.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.4 (CH_3); 128.9, 129.9 (C^o, C^m); 134.5, 137.0 (C^i, C^p). Mass spectrum, m/z (I_{rel}, %): 246 $[M]^+$, 123 (100) $[CH_3C_6H_4S]^+$, 92 $[CH_3C_6H_5]^+$.

2-Bromo-8-methyl-9-(*p*-tolylsulfonyl)-1,2,3,4,4a,9a-hexahydrocarbazol-1-yl acetate (III). Yield 0.135 g (18%), R_f 0.8 (C_6H_6–EtOAc, 2:1). ^{1}H NMR spectrum, (CCl_4–C_6D_6), δ, ppm: 1.60–1.65 m (1H, 4-H_{ax}), 2.05–2.40 m (3H, 3-H, 4-H_{eq}), 2.11 s (3H, CH_3), 2.42 s (3H, CH_3), 2.61 s (3H, CH_3), 2.90 m (1H, 4a-H), 3.80 d.t (1H, 2-H, J = 3.8, 12.0 Hz), 4.20 t (1H, 9a-H, J = 8.0 Hz), 4.68 d.d (1H, 1-H, J = 8.0, 12.0 Hz), 6.80 d (1H, H_{arom}, J = 7.0 Hz), 7.12–7.21 m (4H, H_{arom}), 7.55 d (2H, H_{arom}, J = 8.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.4, 20.8, 21.5 (CH_3); 24.3 (C^4), 31.2 (C^3), 40.1 (C^{4a}), 49.3 (C^2), 69.8 (C^{9a}), 74.3 (C^1); 119.5, 127.1, 127.3, 129.6, 130.9 (C^5, C^6, C^7, C^o, C^m); 134.4, 135.9, 137.6, 140.7, 144.1 (C^{4b}, C^8, C^{8a}, C^i, C^p); 169.8 (C=O). Found, %: C 55.06; H 4.81; Br 16.48; N 2.67; S 6.46. $C_{22}H_{24}BrNO_4S$. Calculated, %: C 55.23; H 5.06; Br 16.70; N 2.93; S 6.70.

9-Acetyl-2,6-dibromo-8-methyl-1,2,3,4,4a,9a-hexahydrocarbazol-1-yl acetate (IV). Yield 0.258 g (37%), mp 189–191°C (from EtOH). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.60 d.q (1H, 4-H_{ax}, J = 3.6, 13.0 Hz), 1.83–2.19 m (2H, 3-H_{ax}, 4-H_{eq}), 1.96 s (3H, CH_3), 2.05 s (3H, CH_3), 2.11 s (3H, CH_3), 2.38 d (1H, 3-H_{eq}, ^2J = 13.0 Hz), 3.77 m (1H, 4a-H), 4.07 d.t (1H, 2-H, J = 3.8, 12.0 Hz), 4.55 t (1H, 9a-H, J = 8.0 Hz), 4.70 d.d (1H, 1-H, J = 8.0, 12.0 Hz), 7.15 s (2H, 5-H, 7-H). Found, %: C 45.58; H 4.09; Br 35.71; N 2.89. $C_{17}H_{19}Br_2NO_3$. Calculated, %: C 45.87; H 4.30; Br 35.90; N 3.15.

9-Acetyl-1,6-dibromo-8-methyl-1,2,3,4,4a,9a-hexahydrocarbazole (VII). Acetyl bromide, 4.9 g (39.83 mmol), was added to a solution of 1 g (2.38 mmol) of hexahydrocarbazole **VI** in 40 ml of chloroform. The mixture was heated for 10 h under reflux, diluted with 50 ml of chloroform, and washed with a 10% aqueous solution of sodium hydrogen carbonate and with water. The organic phase was separated and dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel using benzene as eluent. Yield 0.24 g (26%), mp 164–166°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40–2.30 m (6H, CH_2), 2.25 s (3H, CH_3), 2.50 s (3H, CH_3), 3.64–3.68 m (1H, 4a-H), 3.77 d.d.d (1H, 1-H, J = 4.4, 13.2, 15.0 Hz), 4.45–4.51 m (1H, 9a-H), 7.02 s (1H, H_{arom}), 7.20 s (1H, H_{arom}). Found, %: C 46.33; H 4.19; Br 41.03; N 3.40. $C_{15}H_{17}Br_2NO$. Calculated, %: C 46.54; H 4.43; Br 41.28; N 3.62.

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