Chlorinated Polycyclic Compounds. V. Reactions of Chloro-substituted Dibenzobicyclo[3.2.1]octadienes with Sodium Methoxide

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Displacement of chlorine occurred at 4- and 5-positions only when chloro-substituted dibenzobicyclo[3.2.1]octadienes were treated with sodium methoxide in methanol. Hydrolysis of the methoxy derivatives with a mixture of sulfuric acid and acetic acid gave acetates or ketones of the dibenzobicyclo[2.2.2]octadiene series.

Since attempts to synthetize the ketones 7e and 7f, required for other studies, by acid catalyzed rearrangement\(^1\) of the appropriate dibenzobicyclo[3.2.1]octadiene derivatives\(^2\) were unsuccessful, it was desirable to find a more reactive starting material to effect the conversion. It was found that the chlorides 1o and 1p, when treated with sodium methoxide in methanol, gave methoxy derivatives that were readily hydrolyzed to the desired ketones in quantitative yields. In order to locate the methoxy group in the products and to have an idea of the generality of the reaction, all members of the chloride series 1 were subjected to similar reaction conditions. The results are summarized in Table 1.

In spite of the well-known resistance of bridgehead halides toward nucleophilic substitution, reactions of this kind were observed although they occurred at the less hindered side of the molecule only. The inertness of the 8-chlorine atoms must be ascribed to inability to undergo an Sn2 reaction due to steric reasons and to the lack of sufficient stabilization possibilities required by an Sn1 path. The reactivity of the chlorides unsubstituted at C-5 (1a–1h) was found to be dependent on the substituent at C-8. Displacement of the 4-chlorine was observed when the syn-8-position was unsubstituted (1a–1d), while the syn-8-chloro derivatives (1e–1h) were only epimerized to the endo configuration. The pronounced effect of the syn-8-chlorine is in agreement with the idea that the entering group attacks from the exo side giving exo substitution products, which may then be converted to the endo epimers under thermodynamic control.\(^3\)\(^,4\)

\[\text{Diagram of compounds} \]

\[\text{Table 1: Reactions of chlorides with sodium methoxide} \]

Displacements by Methoxide Ion

4 and 5. Examples of dehalogenations with alkoxides appear in the literature but are best known with bromo compounds.++

The structures of the reaction products are based both on chemical reactions and spectral data. Because hydrolysis of the 4-methoxy derivatives with a mixture of sulfuric acid and acetic acid gave acetates (6) and the 4-chloro-5-methoxy derivatives gave ketones (7), most of which are known,1,8,9,11 it was evident that the 1,8-face of the molecule had remained intact and only the 4- or 5-chlorine atoms participated in the reactions. As the acid hydrolysis still left the 4- and 5-positions as possible sites of the methoxy group in the compounds 3, they were tested with silver acetate and acetic acid. Instead of the expected 4-acetates only rearranged products were obtained: 3a, 3c and 3d gave the same ketones as acid hydrolysis but in the case of 3b and 3e the methoxy acetates 9a and 9b could be isolated. The greater stability of the latter is probably due to steric hindrance caused by the geminal dichloro group. These structures were confirmed by spectroscopic means and by acid catalyzed hydrolysis to the corresponding ketones. Attempts to hydrolyze the acetoxy group in basic media yielded only mixtures while reduction with lithium aluminium hy-

Table 1. Products from the reactions of the chlorides 1a—Ip with sodium methoxide.

<table>
<thead>
<tr>
<th>Starting material</th>
<th>endo-exo ratio</th>
<th>Reaction products</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.  R¹  R²  R³  R⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a    H  H  H  H</td>
<td>35:65</td>
<td>80 % exo-2a</td>
</tr>
<tr>
<td>1b    H  H  H  Cl</td>
<td>25:75</td>
<td>65 % endo-2b</td>
</tr>
<tr>
<td>1c    H  H  Cl  H</td>
<td>50:50</td>
<td>70 % exo-2c</td>
</tr>
<tr>
<td>1d    H  H  Cl  Cl</td>
<td>10:90</td>
<td>80 % endo-2d</td>
</tr>
<tr>
<td>1e    H  Cl  H  H</td>
<td>40:60</td>
<td>80 % endo-1e</td>
</tr>
<tr>
<td>1f    H  Cl  H  Cl</td>
<td>15:85</td>
<td>95 % endo-1f</td>
</tr>
<tr>
<td>1g    H  Cl  Cl  H</td>
<td>30:70</td>
<td>70 % endo-1g</td>
</tr>
<tr>
<td>1h    H  Cl  Cl  Cl</td>
<td>10:90</td>
<td>80 % endo-1h</td>
</tr>
<tr>
<td>1i    Cl  H  H  H</td>
<td>50:50</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>1j    Cl  H  H  Cl</td>
<td>0:100</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>1k    Cl  H  Cl  H</td>
<td>20:80</td>
<td>25 % 4a, 65 % 5</td>
</tr>
<tr>
<td>1l    Cl  H  Cl  Cl</td>
<td>50:50</td>
<td>75 % 3d</td>
</tr>
<tr>
<td>1m    Cl  Cl  H  H</td>
<td>60:40</td>
<td>70 % 3a, 15 % endo-1m</td>
</tr>
<tr>
<td>1n    Cl  Cl  H  Cl</td>
<td>45:55</td>
<td>65 % 3c, 20 % 4b</td>
</tr>
<tr>
<td>1o    Cl  Cl  Cl  H</td>
<td>50:50</td>
<td>90 % 3b</td>
</tr>
<tr>
<td>1p    Cl  Cl  Cl  Cl</td>
<td>50:50</td>
<td>85 % 3e</td>
</tr>
</tbody>
</table>

dride gave the alcohols $\alpha$ and $\beta$. As the 4-methoxy derivatives 2 failed to react with silver acetate and acetic acid, it is evident that the methoxy group in the compounds 3 is at C-5.

The stereostructure at C-4 in the compounds 2 is based on the coupling constants between the 4- and 5-protons.\textsuperscript{18} In the compounds 3 the 4-proton absorbs in the range $\delta 5.47 - 5.99$, which is consistent with an exo-proton. This is clear, if a comparison is made with the spectra of the chlorides 1, where the chemical shifts are: $\delta 5.08 - 5.39$ (endo-4-H), 5.51 - 5.72 (exo-4-H).

The predominant endo configuration of the reaction products, both methoxy derivatives and recovered starting chlorides, shows that epimerization at C-4 occurs in the presence of a base. Epimeric mixtures were used as starting material, because preliminary experiments with pure epimers showed no significant difference of behaviour under the solvolysis conditions.

**EXPERIMENTAL**

For general experimental conditions see Ref. 1.

Preparation of the starting materials. The chlorides 1a,\textsuperscript{4} 1b,\textsuperscript{4} 1c,\textsuperscript{19} 1d,\textsuperscript{1} 1e,\textsuperscript{14} 1f,\textsuperscript{1} 1j,\textsuperscript{1} 1l,\textsuperscript{1} 1m,\textsuperscript{1} 1o\textsuperscript{11} and 1p\textsuperscript{8} have been described earlier.

Preparation of 1g and 1k. The alcohol $\alpha$ (see below) (2.0 g) was refluxed for 10 min with a mixture of 5.0 g of PCl\textsubscript{3} and 5.0 g of POCl\textsubscript{3}. The hot reaction mixture was carefully decomposed with water, extracted twice with chloroform, the chloroform solution washed with NaHCO\textsubscript{3} and water, dried and evaporated. The mixture of the reactions products contained ca. 20% of endo-4,8,8-trichlorodibenzocyclo[3.2.1]octadiene (1g), m.p. 85°C, $\delta 5.61$ (exo-4-H), 4.28 (1-H), 3.97 (5-H) $+8$ Ar-H, $J_{4,5}=5.0$ Hz and 80% of the exo epimer, m.p. 105°C, $\delta 5.17$ (endo-4-H), 4.37 (1-H), 4.08 (5-H) $+8$ Ar-H, $J_{4,5} < 1$ Hz. Similarly, the alcohol $\beta$ gave 10% of 1-endo-4,8,8-tetrachlorodibenzocyclo[3.2.1]octadiene (1h), m.p. 103°C, $\delta 5.73$ (exo-4-H), 4.21 (5-H) $+8$ Ar-H, $J_{4,5} = 4.8$ Hz and 90% of the exo epimer, m.p. 177°C, $\delta 5.13$ (endo-4-H), 4.27 (5-H) $+8$ Ar-H, $J_{4,5} < 1$ Hz. In both cases the epimers were separated by TLC (elution with light petroleum) and crystallized from EtOH. Approximate yields are based on \textsuperscript{1}H NMR.

Preparation of 1i. The chlorides 1i were best obtained by treatment of dibenzocyclo[2.2.2]-octadien-7-one (7a)\textsuperscript{11} with PCl\textsubscript{3} as described above but using a reaction time of 4 h. The product contained ca. 50% of endo-4,5-dichlorodibenzocyclo[3.2.1]octadiene (1i), m.p. 121°C, $\delta 2.65$ (syn-8-H), 2.95 (anti-8-H), 5.53 (exo-4-H), 3.91 (1-H) $+8$ Ar-H and 50% of the exo epimer, $\delta 2.6 - 3.2$ (syn- and anti-8-H), 5.13 (endo-4-H), 3.97 (1-H) $+8$ Ar-H, $J_{4,5}=4.3$ Hz, $J_{4,5}=10.5$ Hz. The epimers could not be separated chromatographically, but the endo epimer was obtained by treatment of the corresponding alcohol (see below) with PCl\textsubscript{3} for 10 min and crystallization from EtOH. The structures of the chlorides 1i were confirmed by successive acetolysis, hydrolysis and oxidation reactions.\textsuperscript{13} Acetolysis of 1i gave 25% of 5-chlorodibenzocyclo[3.2.1]octadien-endo-4-yl acetate, m.p. 159°C, $v_{\text{max}} 1725$ cm\textsuperscript{-1}, $\delta 2.69$ (syn-8-H), 2.81 (anti-8-H), 6.47 (exo-4-H), 3.88 (1-H), 2.03 (OAc) $+8$ Ar-H, $J_{4,5}=4.0$ Hz, $J_{4,5}=11.4$ Hz and 75% of the exo epimer, m.p. 101°C, $v_{\text{max}} 1735$ cm\textsuperscript{-1}, $\delta 2.90$ (syn-8-H), 2.70 (anti-8-H), 6.01 (endo-4-H), 3.99 (1-H), 2.09 (OAc) $+8$ Ar-H, $J_{4,5}=4.0$ Hz, $J_{4,5}=10.0$ Hz. Hydrolysis of the acetates gave the corresponding endo alcohol, m.p. 120°C, $v_{\text{max}} 3330$ cm\textsuperscript{-1}, $\delta 2.60$ (syn-8-H), 2.79 (anti-8-H), 4.96 (exo-4-H), 3.84 (1-H), 2.26 (OH) $+8$ Ar-H, $J_{4,5}=4.4$ Hz, $J_{4,5}=11.0$ Hz and the exo epimer, m.p. 121°C, $v_{\text{max}} 3220$ cm\textsuperscript{-1}, $\delta 2.90$ (syn-8-H), 2.64 (anti-8-H), 4.48 (endo-4-H), 3.93 (1-H), 2.86 (OH) $+8$ Ar-H, $J_{4,5}=4.2$ Hz, $J_{4,5}=11.0$ Hz. On oxidation both alcohols gave the same ketone, 5-chlorodibenzocyclo[3.2.1]octadien-4-one.\textsuperscript{11}

Preparation of 1k. Hydrolysis of 5-anti-8-dichlorodibenzocyclo[3.2.1]octadien-4-yl acetate\textsuperscript{14} and reaction of the epimeric alcohol mixture with PCl\textsubscript{3} for 10 min (see above) gave 10% of endo-4,5-anti-8-trichlorodibenzocyclo[3.2.1]octadiene (1k), $\delta 4.59$ (syn-8-H), 5.51 (exo-4-H), 4.24 (1-H) $+8$ Ar-H and 90% of the exo epimer, m.p. 153°C, $\delta 5.10$ (syn-8-H), 5.32 (endo-4-H), 4.24 (1-H) $+8$ Ar-H. The exo epimer was obtained in a pure state by three recrystallizations from EtOH. The chemical shifts for the endo epimer are from the spectrum of the mixture left in the mother liquor.

Preparation of 1m. The most convenient route to 1m was via acid catalyzed rearrangement\textsuperscript{12} of 5-anti-8-dichlorodibenzocyclo[3.2.1]octadien-4-yl acetate to 7-chlorodibenzocyclo[2.2.2]-octadien-8-one (7c)\textsuperscript{12,11} and reaction of the latter with PCl\textsubscript{3} for 4 h as described above. This reaction gave ca. 15% of endo-4,5-syn-8-trichlorodibenzocyclo[3.2.1]-octadiene (1m), m.p. 110°C, $\delta 4.81$ (anti-8-H), 5.57 (exo-4-H), 4.06 (1-H) $+8$ Ar-H, $J_{4,5}=4.5$ Hz and 85% of the exo epimer, m.p. 130°C, $\delta 4.79$ (anti-8-H), 5.08 (exo-4-H), 4.14 (1-H) $+8$ Ar-H, $J_{4,5}=4.2$ Hz. The epimers were separated by TLC (elution with light petroleum) and crystallized from EtOH.

Reactions of the chlorides 1a - 1p with sodium methoxide. General method: 5.0 g of clean sodium was dissolved in 50 ml of methanol. The chloride (1.0 g) was added and the mixture refluxed for 24 h. The reaction mixture was poured into water, neutralized with HOAc.
and the products were separated by TLC (elution with light petroleum or a 3:1 mixture of light petroleum and chloroform) and purified by crystallization from EtOH. The yields are based on the total amount of the reaction products. The following compounds were obtained:

1a. 80 % of exo-4-methoxydibenzocyclo[3.2.1]octadiene (2a), m.p. 110 °C, δ 2.15 – 2.58 (sym- and anti-8-H), 4.00 (endo-4-H), 3.57 – 3.60 (1-H), 3.50 (OMe) + 8 Ar-H.

1b. 65 % of 1-chloro-endo-4-methoxydibenzocyclo[3.2.1]octadiene (2b), m.p. 196 °C, δ 2.65 (syn-8-H), 2.92 (anti-8-H), 4.53 (exo-4-H), 3.81 (5-H) + 8 Ar-H, J_{4,18} = 5.0 Hz, J_{4,19} = 5.4 Hz.

1c. 70 % of anti-8-chloro-endo-4-methoxydibenzocyclo[3.2.1]octadiene (2c), m.p. 135 °C, δ 4.83 (1-H), 4.16 (endo-4-H), 3.90 (1-H), 3.70 (5-H), 3.57 (O Me) + 8 Ar-H, J_{4,18} = 1.8 Hz.

Id. 80 % of anti-8-dichloro-endo-4-methoxydibenzocyclo[3.2.1]octadiene (2d), m.p. 191 °C, δ 4.57 (syn-8-H), 4.58 (exo-4-H), 4.09 (5-H), 3.60 (O Me) + 8 Ar-H, J_{4,18} = 5.6 Hz.

The chlorides 1e – 1h gave mainly the endo epimer of the starting material. The chlorides 1i and 1j gave complex mixtures containing ca. 60 – 70 % of methoxy derivatives (according to 1H NMR). These mixtures were not fractionated.

1k. 65 % of 5-anti-8-dichlorodibenzocyclo[3.2.1]octadiene (5a), m.p. 117 °C, δ 4.62 (sym-8-H), 3.40 (endo-4-H), 3.60 (exo-4-H), 4.17 (1-H) + 8 Ar-H, J_{4,18} = 17.0 Hz and 25 % of anti-8-chloro-5-methoxydibenzocyclo[3.2.1]-octadiene (4a), m.p. 130 °C, δ 4.63 (syn-8-H), 2.82 (endo-4-H), 3.60 (exo-4-H), 4.13 (1-H), 3.57 (O Me) + 8 Ar-H, J_{4,18} = 16.0 Hz.

II. 75 % of 1-endo-4-anti-8-trichloro-5-methoxydibenzocyclo[3.2.1]octadiene (3d), m.p. 190 °C, δ 4.70 (syn-8-H), 5.65 (exo-4-H), 3.54 (O Me).

Im. 70 % of exo-4-syn-5-methoxydibenzocyclo[3.2.1]octadiene (3a), m.p. 138 °C, δ 4.90 (anti-8-H), 5.47 (exo-4-H) 4.11 (1-H), 3.40 (O Me) + 8 Ar-H, J_{4,18} = 4.8 Hz and 15 % of endo-Im.

In. 65 % of 1-endo-4-syn-8-trichloro-5-methoxydibenzocyclo[3.2.1]octadiene (3c), m.p. 158 °C, δ 4.96 (anti-8-H), 5.60 (exo-4-H) 3.47 (O Me) + 8 Ar-H and 20 % of 1-syn-8-dichloro-5-methoxydibenzocyclo[3.2.1]octadiene (4b), m.p. 147 °C, δ 4.82 (anti-8-H), 2.70 (endo-4-H), 3.34 (exo-4-H), 3.34 (O Me) + 8 Ar-H, J_{4,18} = 17.0 Hz.

Io. 90 % of exo-4,8,8-trichloro-5-methoxydibenzocyclo[3.2.1]octadiene (3b), m.p. 158 °C, δ 5.87 (exo-4-H), 4.40 (1-H), 3.85 (O Me) + 8 Ar-H, m/e 338(54), 303(100).

Jp. 85 % of 1-endo-8,8-tetrachloro-5-methoxydibenzocyclo[3.2.1]octadiene (3e), m.p. 203 °C, δ 5.99 (exo-4-H), 3.87 (O Me) + 8 Ar-H, m/e 372(13), 337(100).

Hydrolysis of the methoxy derivatives 2a – 2d and 3a – 3e. The methoxy compound (0.05 – 0.2 g) was refluxed for 40 min with a mixture of 1.5 g of H₂SO₄ and 3.5 g of HOAc. The mixture was poured into water and the product isolated by ether extraction. 1H NMR and TLC examination showed that the reaction was essentially quantitative in each case. Following compounds were obtained (starting material, hydrolysis product): 2a, 6a; 2b, 6b; 2c, 6c; 2d, 6d; 3a, 7c; 10, 11, 3b, 7e; 3c, 7d, 13, 7d; 3e, 7f.

The new compounds had the following properties: 7,7-dichlorodibenzocyclo[2.2.2]octadien-8-one (7e), m.p. 142 °C, δ 4.92 (1-H), 4.79 (4-H) + 8 Ar-H, m/e 288(8), 178(100) and 1,7,7-trichlorodibenzocyclo[2.2.2]octadien-8-one (7f), m.p. 158 °C, δ 1760 cm⁻¹, δ 4.87 (4-H) + 8 Ar-H, m/e 322(9), 212(100).

Reduction of the ketones 7e and 7f with sodium borohydride and acetylation of the resulting alcohols. A solution of 10 mmol of the ketone (2.68 g of 7e or 3.24 g of 7f) and 0.38 g (10 mmol) of NaN₃ in 100 ml of EtOH was stirred for 80 min at room temperature. The solution was poured into water, HCl added and the aqueous solution extracted twice with ether. The ethereal solution was dried and evaporated. The analytical samples were crystallized from 80 % aqueous EtOH. The ketone 7e gave 7,7-dichlorodibenzocyclo[2.2.2]octadien-8-ol (8a), m.p. 131 °C, δmax 3520, 3520 cm⁻¹, δ 4.73 (1-H), 4.22 (4-H), 4.27 (8-H), 1.77 (OH) + 8 Ar-H, J_{4,18} = 2.6 Hz and 7f gave 1,7,7-trichlorodibenzocyclo[2.2.2]octadien-8-ol (8b), m.p. 172 °C, δmax 3540, 3560 cm⁻¹, δ 4.20 (4-H), 4.37 (8-H), 2.04 (OH), J_{4,18} = 2.6 Hz.

The alcohol 8a (0.2 g) refluxed for 80 min with a mixture of 10 ml of Ac₂O and 1 ml of pyridine, gave the acetate 8b, m.p. 139 °C, δmax 1743 cm⁻¹, δ 4.70 (1-H), 4.23 (4-H), 5.29 (8-H), 2.00 (OAc) + 8 Ar-H, J_{4,18} = 2.6 Hz. Similarly, 8b gave the acetyl 8b, m.p. 170 °C, δmax 1754 cm⁻¹, δ 4.23 (4-H), 5.44 (8-H), 2.02 (OAc) + 8 Ar-H, J_{4,18} = 3.6 Hz. The acetates were crystallized from EtOH.

Acetylation of the methoxy derivatives 3a – 3e. The compound 3b (0.68 g, 2.0 mmol) was refluxed for 10 min with 0.40 g (2.4 mmol) of AgOAc and 20 ml of HOAc. Acetic acid was removed under reduced pressure, the residue dissolved in acetone, the solution filtered and evaporated. According to 1H NMR, the mixture contained ca. 30 % of unreacted 3b, 20 % of the ketone 7e and 50 % of an unknown acetate. The components were separated by TLC (elution with a 1:1 mixture of light petroleum and chloroform). The last compound was crystallized from EtOH to give 7,7-dichloro-8-methoxydibenzocyclo[2.2.2]octadien-8-yl acetate (9a), m.p. 203 °C, δmax 1740 cm⁻¹, δ 4.62 (1-H), 5.33 (4-H), 3.35 (O Me), 1.81 (OAc) + 8 Ar-H, m/e 319 (M+4 8, 1.78 (100).

Similarly, 3e gave 30 % of unreacted starting material, 10 % of the ketone 7f and 60 % of 1,7,7-trichloro-8-methoxydibenzocyclo[2.2.2]octadien-8-yl acetate (9b), m.p. 160 °C, δmax 1750 cm⁻¹, δ 5.42 (4-H), 3.41 (O Me), 1.85 (OAc) + 8 Ar-H, m/e 353 (M+4 3, 0.7), 212(100).
The only reaction products from the compounds 3a, 3c and 3d were the ketones 7c, 7d and 7d, respectively.

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REFERENCES


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