1,3-Bridged Aromatic Systems. X. Stereospecific Reductions with Lithium Aluminum Deuteride[1]

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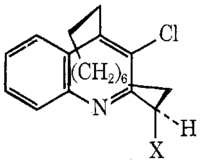
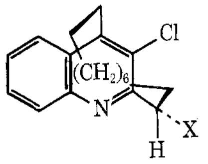
Although meta cyclophanes of type **1a**, **1b**, **2a**, and **2b** are quite resistant to nucleophilic substitution reactions,[2] we have observed that they are readily reduced to **1c** by $LiAlH_4$. In a preliminary experiment we observed that **1b** did not react with 1 equiv (0.25 molar equiv) of $LiAlH_4$ in dry ether, but gave **1c** in 54% yield when an excess (3.5 molar equiv) of $LiAlH_4$ was employed. Since we wished to prepare the monodeuterated cyclophanes **1d** or **2d** for other studies, we have examined the reaction of **1a**, **1b**, **2a**, and **2b** with $LiAlD_4$. In each case a monodeuterated product (99% monodeuterio by pmr and/or mass spectral analysis) was obtained (62, 74, 66, and 21%[3] yields, respectively), and in every case the product was the syn isomer **1d**. Thus, complete retention of configuration occurred with **1a** and **1b** and complete inversion of configuration occurred with **2a** and **2b**. While displacement reactions of this type normally[4] occur with inversion of configuration, reductions with retention of configuration as well as nonselective reduction have been reported.[5]



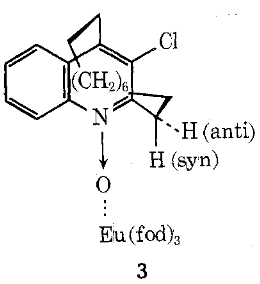
1 (syn)



2 (anti)

a, X = Br
b, X = p-$CH_3C_6H_4SO_3$
c, X = H
d, X = D

Assignment of the syn and anti hydrogens in **1c** by comparison of their pmr signals at 60 MHz with those of the derived *N*-oxide, as used successfully for other derivatives in the system,[2a] was not possible, since the four benzylic protons in **1c** and in the corresponding *N*-oxide of **1c** are not sufficiently resolved at 60 MHz. Definite assignments were possible, however, for the *N*-oxide of **1c** by pmr (100 MHz) using the chemical shift reagent $Eu(fod)_3$-d_{27}.[6] A plot of the pmr signals of **3** *vs.* *R* in which the ratio *R* ($[Eu(fod)_3$-$d_{27}]/[N$-oxide$]$) was varied at constant volume (*i.e.*, [*N*-oxide] was constant) is shown in Figure 1. This model predicts that the syn proton (and the peri H) should show larger downfield shifts with larger *R* values than the anti proton, since the syn proton not only occupies a position closer to europium, but is also expected to have an angle ϕ_{syn} (defined by the europium-substrate bonding axis and the syn proton) which is smaller than ϕ_{anti}.[7] These predictions are corroborated by the slopes of the lines shown in Figure 1. The syn proton (c) exhibits a slope of 8.9 ± 0.6 and the peri hydrogen (a) 11.3 ± 0.4, while the anti proton exhibits a slope of 2.6 ± 0.2. Applying this same technique to the monodeuteriocyclophane **1d**, obtained from **1a**, **1b**, **2a** and **2b**, showed complete absence of syn H; the anti proton was present and integrated for one proton compared with the four aromatic protons.



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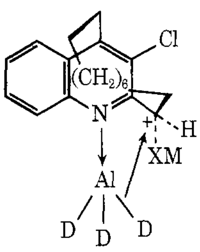
Additional evidence for the syn structure **1d** (obtained from **1b**) was obtained by pmr studies at 100 and 270 MHz. At 100 MHz the four benzylic protons of **1c** appear as a multiplet at δ 3.8–2.8; the corresponding spectrum of **1d** shows a three-proton absorption at δ 3.8–3.2, with loss of the upfield component observed for **1c**. The 100-MHz spectrum of the *N*-oxide of **1c** shows a four-proton absorption at δ 3.9–3.2, while the *N*-oxide of **1d** shows a three-proton absorption at δ 3.7–3.2 with loss of the downfield component observed for the *N*-oxide of **1c**. By analogy to previously reported[2a] examples of large chemical shift changes of syn protons in going from the free base to the corresponding *N*-oxide, the upfield proton in **1c** and the downfield proton in the *N*-oxide of **1c** are assigned to the syn proton, which is absent in **1d**. At 270 MHz the pmr spectrum of the unlabeled *N*-oxide of **1c** was well resolved and showed the syn proton centered at δ 3.71 (octet, $J_{AB(gem)}$ = 12–13, $J_{AC(cis)}$ = 4, $J_{AD(trans)}$ = 3 Hz, all *J*'s first order), one proton at the other benzylic position centered at δ 3.45 (octet, $J_{AB(gem)}$ = 13–14, $J_{AC(cis)}$ = 10, $J_{AC'(trans)}$ = 4 Hz, all *J*'s first order), and two benzylic protons centered at δ 3.3 (multiplet). The downfield absorption at δ 3.71 was completely absent in the labeled *N*-oxide derived from **1d** which is consistent with the conclusion that all of the deuterium was at the syn position as shown in **1d**. The anti proton has been assigned resonance at δ 3.3, since the splitting pattern in that region is simplified in the labeled compound.

While we can make no definitive statement concerning the mechanism[8] and stereoselectivity of the reduction process, the requirement of excess $LiAlH_4$ suggests that a complex of reagent with nitrogen prior to reduction is possible, as illustrated in **4** and **5**.



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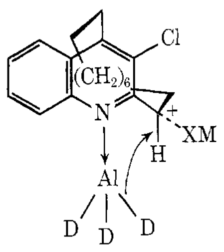

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Experimental Section

Reductions with $LiAlD_4$. A. In a typical experiment a solution of syn tosylate **1b**[2a] (6.43 g, 13.6 mmol) in dry diethyl ether (120 ml) was heated under nitrogen at reflux for 24 hr with $LiAlH_4$ (17.4 mmol).[12] The reaction mixture was quenched with D_2O (3 ml) and then acidified with 5% hydrochloric acid (150 ml). The extract was washed (saturated sodium bicarbonate) and then dried ($MgSO_4$) and concentrated. The resulting oil (4.4 g) was chromatographed [260 of g alumina, 0.5% diethyl ether-petroleum ether (bp 60-90°) to 100% ether as eluent] to give **1d**: 3.08 g (75% yield); mp 81-82° from ethyl acetate; mmp[9] 81-82°; mass spectral analysis showed 99+% monodeuterio species.

The *N*-oxide of **1d** was prepared by oxidation of **1d** with *m*-chloroperbenzoic acid:[2,10] 74% yield; mp 122.5-123.5° (from acetone) (lit.[11] mp 125-127°); mmp 122.5-123.5°.

B. In an alternate procedure used for **1a**, **2a**, and **2b**[2a] dry (distilled from $LiAlH_4$) tetrahydrofuran (10-15 ml) was used as solvent (16 hr, 66.5 hr for **2a**). The reduced cyclophane **1d** was purified by preparative tlc [silica gel, 25% diethyl ether-petroleum ether (bp 30-60°)].

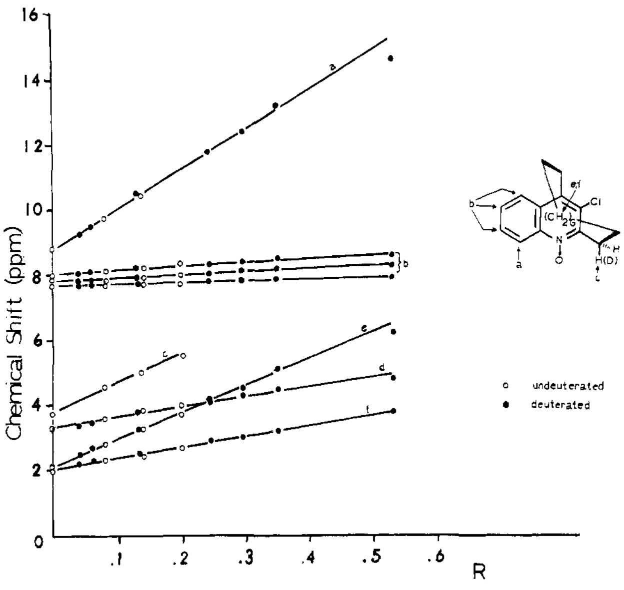

Figure 1.

Registry No.—**1a**, 25859-37-4; **1b**, 37781-25-2; **1c**, 22200-39-1; **1c** *N*-oxide, 25907-81-7; **1d**, 51794-47-9; **1d** *N*-oxide, 51820-05-4; **2a**, 42880-45-5; **2b**, 37781-31-0; $LiAlD_4$, 14128-54-2.

References and Notes

(1) This work was supported by the National Science Foundation (Grant GP-35429).

(2) (a) W. E. Parham, K. B. Sloan, K. R. Reddy, and P. E. Olson, *J. Org. Chem.*, **38**, 927 (1973); (b) *ibid.*, **39**, 172 (1974).

(3) The major product had the same R_f value as anti alcohol **2** (X = OH) but fluoresced with a different color on silica gel; however, the product was not further characterized.

(4) (a) E. L. Eliel, *J. Amer. Chem. Soc.*, **71**, 3970 (1949); (b) A. Streitweiser, *ibid.*, **75**, 5014 (1953); (c) G. K. Helmkamp, C. D. Joel, and H. Sharnan, *J. Org. Chem.*, **21**, 844 (1956).

(5) V. M. Micovic and M. L. Mihailovic, "Lithium Aluminum Hydride in Organic Chemistry," Izdacko Preduzece, Belgrade, 1955, pp 116–118.

(6) B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan, and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 3281 (1971).

(7) For a recent review on nmr shift reagents see A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, **73**, 553 (1973).

(8) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, pp 88–89.

(9) W. E. Parham, R. W. Davenport, and J. B. Biasotti, *Tetrahedron Lett.*, 557 (1969).

(10) Use of hydrogen peroxide in acetic acid was avoided so as to minimize possible D-H exchange of benzylic protons. *Cf.* W. E. Parham and P. E. Olson, *Tetrahedron Lett.*, 4783 (1973).

(11) W. E. Parham, R. W. Davenport, and J. B. Biasotti, *J. Org. Chem.*, **35**, 3775 (1970).

(12) The hydride was used as an unfiltered slurry.

Carbenium Ion Rearrangements in the Alkylation of Tertiary Halides with Trimethylaluminum

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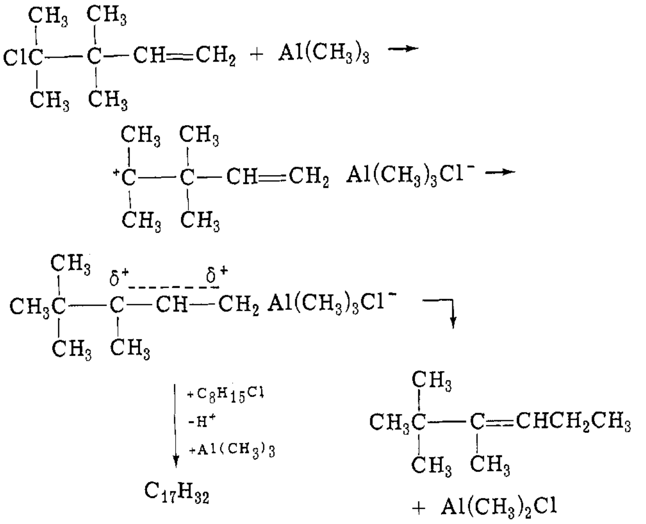
In the course of our fundamental studies on cationic isomerization polymerization we were interested in the synthesis of 3,3,4,4-tetramethyl-1-pentene, which we hoped to obtain by methylating 4-chloro-3,3,4-trimethyl-1-pentene with Me_3Al. The rapid, quantitative methylation with Me_3Al of tertiary chlorines to quaternary carbons has recently been described.[1]

Interestingly, instead of the desired product we obtained 2,2,3-trimethyl-3-hexene, most likely by the following route.



$$ClC(CH_3)_2C(CH_3)_2CH{=}CH_2 + Al(CH_3)_3 \rightarrow$$

$$^{+}C(CH_3)_2C(CH_3)_2CH{=}CH_2\ Al(CH_3)_3Cl^- \rightarrow$$

$$CH_3C(CH_3)_2\overset{\delta^+}{C}(CH_3)\text{---}\overset{\delta^+}{C}H\text{---}CH_2\ Al(CH_3)_3Cl^- \rightarrow$$

$$\xrightarrow[+Al(CH_3)_3]{+C_8H_{15}Cl,\ -H^+} C_{17}H_{32}$$

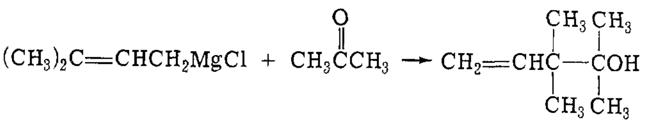
$$CH_3C(CH_3)_2\text{---}C(CH_3){=}CHCH_2CH_3 + Al(CH_3)_2Cl$$

The initially formed carbenium ion rearranges to the more stable tertiary, allylic ion. This carbenium ion subsequently reacts with the counterion to give the thermodynamically more stable internal olefin.

In addition to 2,2,3-trimethyl-3-hexene, a second product of overall composition $C_{17}H_{32}$ was also obtained. While conclusive structural analysis could not be carried out, it is presumed that this product is a methylated dimer.

According to these findings allylic rearrangement by methide shift and dimerization is faster than methylation of the carbenium ion by the Me_3AlCl^- counteranion. The relatively slow methylation of carbenium ions with Me_3AlCl^- is important in cationic polymerization and might account for the formation of high molecular weight polymers by the faster propagation (dimerization) step.

The tertiary chloride used in the above scheme was prepared from the corresponding tertiary alcohol; no evidence for rearrangement during this step has been detected. The tertiary alcohol in turn was obtained by an unusual Grignard (rearrangement) synthesis found in our laboratory. Thus the reaction between γ,γ-dimethylallylmagnesium chloride and acetone yields 4-hydroxy-3,3,4-trimethyl-1-pentene. Evidently the internal C of the allylic system rather than the C bonded to the -MgCl reacts with the carbonyl function. Similar rearrangements during Grignard reactions of allylmagnesium halides have been described.[2,3]



$$(CH_3)_2C{=}CHCH_2MgCl + CH_3\overset{O}{\overset{\|}{C}}CH_3 \rightarrow CH_2{=}CHC(CH_3)_2\text{---}C(CH_3)_2OH$$

Experimental Section

General. Gas chromatographic analysis was carried out with an HP-5750 gas chromatograph. Molecular weights were determined using a Chromalytics MC-2 mass chromatograph. Nmr analysis was done using a Varian T-60 spectrometer. Microanalysis was done by Galbraith Laboratories, Knoxville, Tenn. Distillations were carried out using a Nester-Faust adiabatic spinning band column.

Synthesis of 4-Hydroxy-3,3,4-trimethyl-1-pentene. To synthesize this previously unknown alcohol, we adapted the procedure of Dreyfuss[4] for the Grignard reaction. To 0.50 mol of magnesium turnings in 100 ml of ether was added γ,γ-dimethylallyl chloride (0.05 mol) in 25 ml of ether. After the reaction was proceeding vigorously, a solution of the remaining chloride (0.45 mol)