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CYCLOPENTANONES—XIII[a]

THE PROTON DONOR DEPENDING STEREOSELECTIVITY OF LITHIUM AMMONIA REDUCTION OF 2,3-DIMETHYL-4-HYDROXY-2-CYCLOPENTENONE

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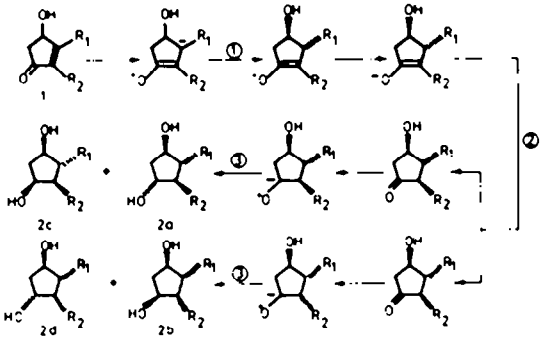
Abstract—The stereochemistry of the lithium-liquid ammonia reduction of 2,3-dimethyl-4-hydroxy-2-cyclopentenone is discussed as a function of the acidity of the proton donor. It is shown that the configuration of the resulting 2,3-dimethyl-1,4-dihydroxycyclopentene is determined by competing intra- and intermolecular protonation.

The lithium-liquid ammonia-alcohol reduction of 2,3-disubstituted - 4 - hydroxy - 2 - cyclopentenones (analogues of **1** with functionalised side chains) is an important step in our prostaglandin synthesis.[1-3] In previous papers the stereochemistry and configurational assignment of the resulting 2,3 - dialkyl - 1,4 - cyclopentanediols was described,[4-6] it was noted that the stereochemical outcome of the reduction depended on the reaction parameters. In order to elucidate the reaction mechanism, the influence of the acidity of the proton source and to a lesser extent the effect of concentration were investigated on model compound **1**.

As can be seen in Table 1 the reduction of 2,3 - dimethyl - 4 - hydroxy - 2 - cyclopentenone **1** predominantly yields two diastereoisomers with trans **2a** or cis **2b** methyl substituents. The mechanism of the reduction can be subdivided into three protonation steps (Scheme 1). The stereochemical outcome of the first and third steps (for both >95% trans OH–CH_3, the yield of **2c** being arbitrarily divided) is in accordance with existing views on protonation of epimeric carbanions (β position) in the reduction of enones and epimeric dianions in the reduction of cyclic ketones.[7]

The second protonation is subject to the acidity of the proton donor (see Table 1) which clearly determines the ratio of the diastereoisomers **2a** and **2b**. One could rationalise the formation of **2a** and **2b** by invoking an equilibration of the saturated ketone before further reduction (third step). That this does not occur is proven by the experiments given in Scheme 2. Treatment of both the pure 2,3-dimethylcyclopentanones **3a** and **3b**[12] with lithium phenolate as base in liquid ammonia leads to the equilibrium mixture **3a**:**3b** in a ratio of 85:15. On the other hand reduction of **3b** with lithium-liquid ammonia-phenol yields as the sole product (GC analysis) the alcohol



Scheme 1

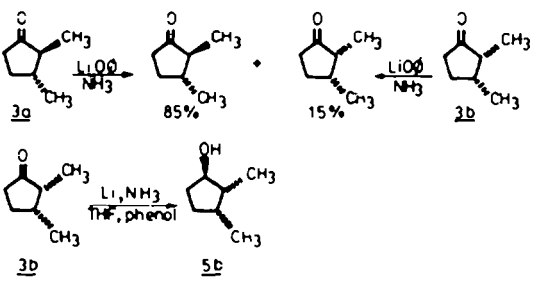
*Part XII: *Bull. Soc. Chim. Belges* in press

Table 1

1	2a	2b	2c	1 & diol trans alkyl	1 & diol cis alkyl
phenol	67 %	26 %	7 %	74	26
methanol	62 %	28 %	10 %	72	28
ethanol	52 %	43 %	5 %	57	43
i.propanol	33 %	60 %	7 %	40	60
t.butanol	21 %	74 %	5 %	26	74

Total yield : 95 %

Concentration on substrate : 10^{-1} mol/liter.



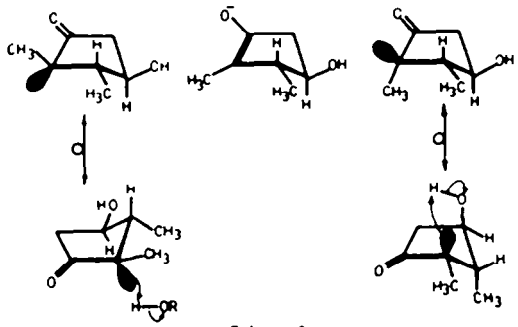
Scheme 2

5b. These facts prove that reduction is much faster than equilibration, which should have taken place through enolate anion formation.

In order to evaluate the role of the hydroxyl function in **1** as a potential proton source, the reduction of 2,3-dimethylcyclopentenone **4** was studied under identical conditions with the same set of proton donors (Table 2). Comparison of the reduction of **1** and **4** shows that the presence of the hydroxyl function has an influence, not only on the stereochemical outcome, but also on the total yield of complete reduction products (saturated alcohol). For compound **1** a reversal of the ratio's of reduction products **2a** + **2c** (Σ % CH_3 trans) and **2b** (Σ % CH_3 cis) was observed. On the other hand the ratio of reduction products of **4**, the diastereoisomeric alcohols **5a** + **5c** (Σ % CH_3 trans) and **5b** (Σ % CH_3 cis) was practically constant, the more stable isomer **5a** was formed preferentially.

The results can be explained as a function of the pK_A value of the proton donor. The pK_A scale in liquid ammonia differs largely from that in water,[13] acetone has a pK_A value in the range of that of ethanol and is more acidic than t-butanol. Indeed t-butanol is frequently added as proton source for reduction to the saturated ketone stage since the second protonation step is then very slow. However further reduction, although in lower yield, is sometimes observed. This is also the case for the reduction of **4** (yield of alcohols 31%) with t-butanol as proton source, which is probably due to the fact that an enolate anion of a α,α-disubstituted ketone is a stronger base than the acetone enolate anion. The high yield conversion of **1** to the saturated alcohols (**3a**, **b**, **c**) in the presence of t-butanol shows that the 4-hydroxyl group serves as a proton source.

The stereochemical outcome of the reduction of **1** is determined by competition between intra- and intermolecular protonation. With the more acidic proton donors intermolecular reaction occurs. It is generally accepted that the relative stabilities of transition states for the product determing protonation of epimerisable carbanions usually reflects qualitatively the relative stabilities of the products[8] (Scheme 3). With less acidic external proton sources the competing intramolecular protonation becomes effective. It is obvious that this results in cis configuration of the methyl groups, because of the stereochemical outcome (OH–CH_3 trans, Scheme 1) of the first reduction step.

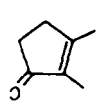
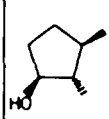
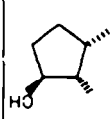
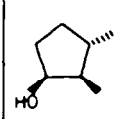
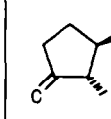


Scheme 3

Additional proof of the occurrence of internal 1,3-protonation was obtained by the reduction of **1** with methanol as proton donor under dilute conditions (10^{-3} mol l^{-1}), the relative ratio of diastereoisomers was **2a** 35%, **2b** 62% and **2c** 3%. Comparison with the result (MeOH) in Table 1 for substrate concentration 10^{-1} mol. l^{-1} is clearly demonstrative.

The results provide substantial evidence for the presence in **1** of the 4-hydroxyl group as such and not as an anion. However it is not clear why expulsion of the hydroxyl group does not compete with the first protonation step, as it is known that allylic hydroxyl groups are cleaved under these reaction conditions.[14] Analogous stereochemical results are obtained for homologues of **1** with functionalised side chains attached through a methylene unit on the cyclopentenone ring, the total yields are however in the range of 60%. Further investigations are in progress.

Table 2

 4	 5a	 5b	 5c	 3a	% alcohol trans alkyl	% alcohol cis alkyl
phenol	60 %	19 %	4 %	17 %	77	23
methanol	72 %	20 %	2 %	6 %	78	22
ethanol	72 %	23 %	-	5 %	76	24
i.propanol	48 %	19 %	3 %	30 %	72	28
t.butanol	17 %	7 %	7 %	69 %	77	23

Total yield ~ 95 %

Concentration on substrate = 10^{-1} mol/liter.

EXPERIMENTAL

2,3-Dimethyl-1,4-cyclopentanediol **2a, 2b, 2c**. Compound **1**[11] (1 g, 8 mmol) is dissolved in anhydrous alcohol (20 mmol) and dry tetrahydrofuran (10 ml) was added to liquid ammonia (80 ml, distilled from sodium). Lithium (0·44 g, 64 mmol) was added in small pieces over a period of 10 min. After stirring 1 h the excess lithium was destroyed with ammonium chloride, the ammonia evaporated off, ether added and the inorganic salts filtered off. After acidifying with dil HCl, the water layer was extracted with ether (6×), followed by continuous extraction (24 h). The combined ether extracts were dried (Na_2SO_4) and evaporated. Yield 97%. TLC R_f 0·2 (ethyl acetate). All experiments were carried out in duplicate.

1,4-Diacetoxy-2,3-dimethylcyclopentanes. A soln of the diols **2a, 2b, 2c** in acetic anhydride (4 ml) and pyridine (4 ml) was warmed at 70°C for 2 h. The reaction mixture was poured on to ice and extracted (after 30 min) with n-pentane. The extract was washed with 2% aq HCl, dried (Na_2SO_4) and evaporated. Yield 95%.

2,3-Dimethylcyclopentanols **5a, 5b, 5c**. Reduction of **4** and conversion of **5** to the acetate were carried out under the same conditions as described for **1**.

Determination of the isomeric distribution (Tables 1 and 2). The crude diacetates **2a, 2b, 2c** were analysed by GC, using a Varian 1400, on OV-17 (6% on Chromosorb W, 3m, linear temperature programme 140°C, 4°C min^{-1}). A fourth isomer present (< 1%) was not taken into account.[5] The crude acetates **5a, 5b, 5c** were measured in the same way.

Configurational assignment of the **5** isomers follows from ^{1}H NMR spectroscopic results.[17]

Equilibration of trans 2,3-dimethylcyclopentanone **3a** *and cis 2,3-dimethylcyclopentanone* **3b**. A soln of **3a** or **3b** (0·5 g, 4·5 mmol) in dry tetrahydrofuran (5 ml) was added to liquid ammonia (40 ml, distilled from sodium). A catalytic amount of lithium phenolate in dry tetrahydrofuran (2 ml) was added and the soln stirred for 7 h. The reaction mixture was quenched with dry ammonium chloride, the ammonia was evaporated and dry ether continuously added to keep a constant volume. The inorganic salts were filtered off and the ether evaporated. The isomeric mixture was analysed by GC on Carbowax 20M (10% on Chromosorb W, 6 m).

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