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ALKALI METAL-LIQUID AMMONIA REDUCTION OF γ-LACTONES TO DIOLS AND CYCLIC HEMIACETALS : STEREOCHEMICAL INFLUENCE BY THE NEIGHBOURING GROUP ON THE NATURE OF THE PRODUCTS

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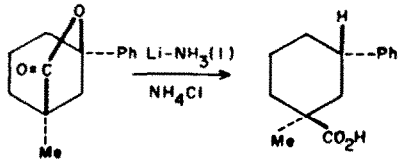
Abstract - Lithium or sodium-liquid ammonia reduction of 3-hydroxy-1,3-dimethylcyclohexane-1,3-carbolactones (5), (6) and (7) with or without a C-2 equatorial substituent gives the respective diols (8), (9) and (10), whereas the lactones (11) and (12), having a C-2 axial substituent produce the respective cyclic hemiacetals (13) and (14) as the sole products. A possible mechanism has been suggested for rationalisation of these results.

The reduction of esters to alcohols by alkali metals and liquid ammonia in the presence of alcohol or ammonium chloride as a proton donor is a well established method[1]. Recently, an efficient procedure for the reduction of $-CONH_2$ group to $-CH_2OH$ has also been reported[2] by sodium and liquid ammonia. In spite of an early report[3] on the transformations of some steroidal spiro γ-lactones to spiro hemiacetals and diols by metal-ammonia reduction, little attention has been paid to delineate the scope of this reduction to other γ-lactones. In connection with a study[4] on the mechanism of the stereoselective reductive cleavage of benzylic γ-lactones to the respective acids (e.g. 1→2), we investigated metal-ammonia reduction of a few structurally related non-benzylic γ-lactones. We report here the results of that study revealing that the products from the reduction of these γ-lactones are dramatically influenced by the stereochemistry of a C-2 substituent.



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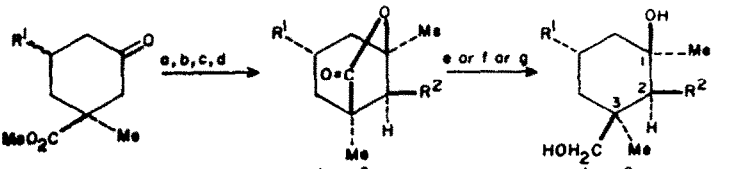
RESULTS AND DISCUSSION

The γ-lactones (5) and (6), prepared by condensation of methylmagnesium iodide with the keto-esters (3)[4] and (4)[4] followed by lactonisation, on reduction with an excess of lithium and anhydrous ammonia using ammonium chloride as the proton donor, led to the respective diols (8) and (9) in excellent yield. Repeating the reactions of 5 and 6 with sodium-ammonia and ethanol again gave the respective diols in ca 76% yield. Under identical conditions the C-2 equatorial benzyl lactone (7)[5] afforded the diol (10) in 69-82% yield (Scheme-1). The structures of these diols were confirmed by direct comparisons with the samples prepared by $LiAlH_4$ reduction of the corresponding lactones.

Scheme-1

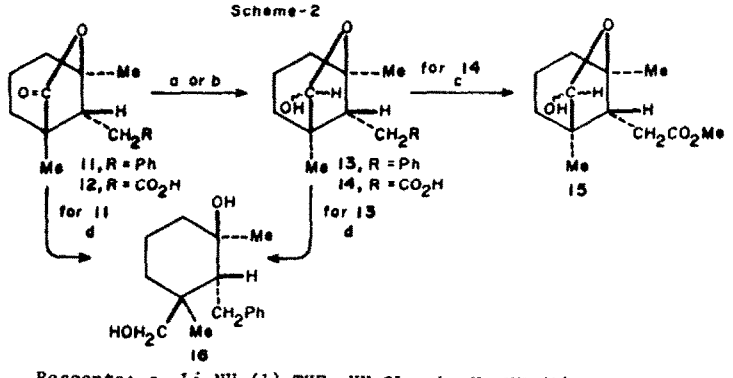


3, R^1 = H
4, R^1 = α-Me and β-Me in a ratio of ca 80:20
5, R^1 = R^2 = H
6, R^1 = Me ; R^2 = H
7, R^1 = H; R^2 = CH_2Ph
8, R^1 = R^2 = H
9, R^1 = Me; R^2 = H
10, R^1 = H, R^2 = CH_2Ph

Reagents: a, MeMgI-Et_2O; b, p-TsOH-C_6H_6(Δ); c, KOH-H_2O (Δ);
d, 6N-HCl (Δ); e, Li-NH_3 (l)-THF, NH_4Cl;
f, Na-NH_3 (l)-THF, EtOH; g, $LiAlH_4$-Et_2O

In contrast, the lactones (11)[5] and (12)[6], having an axial C-2 substituent, on lithium or sodium liquid ammonia reduction afforded the respective cyclic hemiacetals (13) and (14) in excellent yields, in a single stereoisomeric form in each case. The acid (14) was characterised through the corresponding methyl ester (15) (CH_2N_2). The IR and ^1H NMR spectral data of 13 and 15 are in complete agreement with the assigned structures. However, the stereochemistry of the newly generated hemiacetal chiral centre remained unidentified. The structure of 13 was further confirmed through its transformation to the diol 16 by reduction with $LiAlH_4$.

Scheme-2



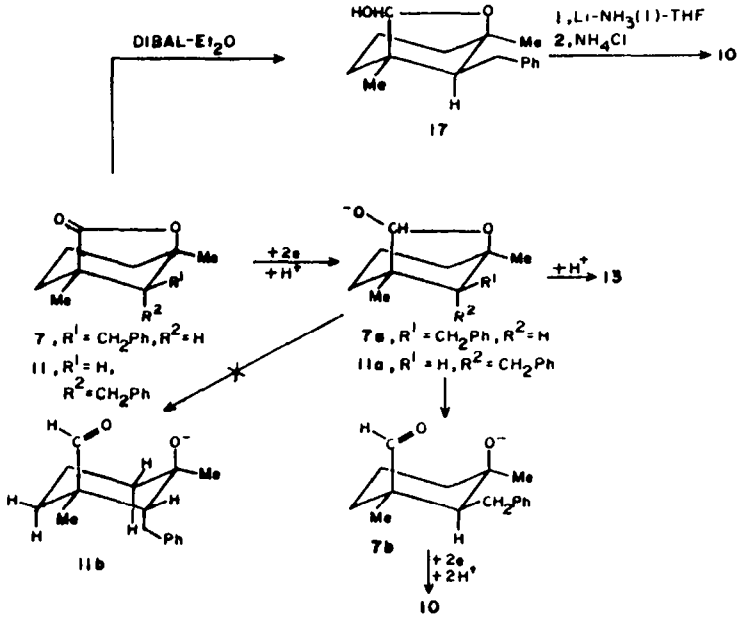
11, R = Ph
12, R = CO_2H
13, R = Ph
14, R = CO_2H
15
16

Reagents: a, Li-NH_3(l)-THF, NH_4Cl: b, Na-NH_3(l)-THF, EtOH;
c, CH_2N_2-Et_2O; d, $LiAlH_4$

The present results clearly indicate that in metal-ammonia reduction of 3-hydroxy-1,3-dimethylcyclohexane-1,3-carbolactones, (5)-(7) with or without a C-2 equatorial substituent gives the respective diols, whereas those having C-2 axial substituent (11) and (12) produce the respective cyclic hemiacetals. In view of these observations, the dramatic influence of the stereochemistry of the neighbouring C-2 substituent, for example, in the diastereoisomeric lactones 7 and 11, on the formation of the respective diol (10) and the cyclic hemiacetal (13) in metal-ammonia reduction, is not altogether surprising. These and the related results of our findings on the metal-ammonia reduction of the γ-lactones may be explained in the following way. In the course of the reduction of lactones, e.g. 7 and 11, by alkali metals-ammonia using ammonium chloride or alcohols as proton donors, the first step may be a Bouveault-Blanc type reaction[1b], similar to that follows in the reduction of esters to alcohols[7], leading rapidly to the respective cyclic hemiacetal ions 7a and 11a. The former possibly undergoes rate determining dissociation to generate free carbonyl derivative 7b (Scheme-3), resulting in it's further reduction to the diol (10) by electron addition

and protonation processes. The comparative stability[8] of the intermediate hemiacetal anion (11a) from the C-2 axially benzyl substituted lactone (11), with respect to that of it's ring-opened form (11b) makes it reluctant for ring opening, thereby leading to the cyclic hemiacetal (13) [or the hemiacetal (14) from the γ-lactone-acid (12)] as the only product. An evidence in support of this postulation was obtained by a facile lithium-ammonia reduction of the C-2 epimeric hemiacetal (17), prepared through reduction of the lactone (7) with DIBAL, to the respective diol 10, in 81% yield.

Scheme-3



In conclusion, the present investigation clearly shows the potential of the alkali metal-liquid ammonia reduction for transformation of γ-lactones to the respective diols or the cyclic hemiacetals, depending upon the stereochemistry of the neighbouring substituent.

EXPERIMENTAL

The compounds described are all racemates, Melting points, taken in open capillary, are uncorrected. IR spectra were recorded on a Perkin-Elmer model 298 spectrometer. ^{1}H NMR spectra were taken in CCl_4 (unless specified) on a Varian Associates Model T-60A spectrometer with TMS acting as internal standard (δ =0 ppm). Elemental analyses were performed by Mr. P.P. Bhattacharyya of this laboratory. Column chromatography was performed on 'Brockman' neutral alumina (B.D.H. India) petroleum and light petroleum refer to the fractions bp 60-80°C and 40-60°C, respectively.

c-3-Hydroxy-1-t-3-dimethylcyclohexane-r-1,3-carbolactone (5). To a well-stirred ice-cold solution of the keto-ester 3[4] (10.0 g, 0.056 mol) in dry Et_2O (50 ml) a solution (Et_2O) of MeMgI [prepared from Mg turnings (1.83 g, 0.076 g atom), MeI and Et_2O (50ml)] was added dropwise for 2 h. The mixture was stirred at 0–5°C for an additional 1 h and finally refluxed for 1 h. It was decomposed (at 0°C) with dropwise addition of an ice-cold saturated NH_4Cl aq. and extracted with Et_2O (4 x 50 ml); the combined Et_2O layer was washed with H_2O, $Na_2S_2O_3$ aq. (5%) and finally with H_2O, and dried (Na_2SO_4). The residual mobile liquid after evaporation of the solvent was dissolved in benzene (150 ml) and refluxed for 12 h under a Dean-Stark water separator with p-TsOH.H_2O (0.5 g). The mixture was cooled and washed with H_2O. The crude product, after evaporation of the solvent, was hydrolysed with ethanolic-KOH (10%, 80 ml). Most of the ethanol was distilled-off under reduced pressure after dilution of the reaction mixture with H_2O (50 ml); the unhydrolysed neutral material was extracted with Et_2O. The aq. layer was acidified with an excess of 6N HCl and heated on a steam-bath for 15 min after which the cooled mixture was extracted with Et_2O. The combined Et_2O extract was washed with Na_2CO_3 aq. (5%), H_2O and finally dried (Na_2SO_4). Removal of the solvent afforded the lactone 5 (5.97 g, 66%) as a colourless liquid which on distillation [100°C (bath temp.) at 0.2 mm Hg] solidified, mp 47°C (light petroleum); ν_{max} (KBr) 1760cm^{-1}; ^{1}H NMR δ 1.13 (3H, s, CH_3) and 1.40 (3H, s, CH_3). Anal. calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found : C, 70.1; H, 9.2%.

c-3-Hydroxy-1-t-3,t-5-trimethylcyclohexane-r-1,3-carbolactone (6). The crude reaction product from the epimeric keto-ester mixture 4 (10 g, .05 mol) with MeMgI, prepared from Mg (2 g, 0.08 g atom) in Et_2O (20 ml), on treatment with p-TsOH.H_2O in boiling benzene followed by saponification with ethanolic KOH (10%, 100 ml), as described for 5, and relactonisation with 6N HCl afforded 6 (2.7 g, 30%), mp 67°C (light petroleum); ν_{max} (KBr) 1760cm^{-1}; ^{1}H NMR δ 1.00 (3H, d, J = 6 Hz, $CHCH_3$), 1.18 (3H, s, CH_3) and 1.43 (3H, s, CH_3). Anal. calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found : C, 71.4; H, 9.6%.

Reduction of the Lactone 5 : 1-t-3-Dimethyl-c-3-hydroxymethyl-r-1-cyclohexanol (8): (A) With Li-NH_3. To a well-stirred solution of 5 (77 mg, 0.5 mmol) in dry THF (5 ml) and dry liquid NH_3 (ca 50 ml) distilled from Na, was added freshly scrapped Li-wire (24.5 mg, 3.5 mg. atom) in small portions during ca 5 min. After another 5 min the blue colour was discharged by cautious addition of powdered NH_4Cl. After evaporation of NH_3 the residue was diluted with H_2O (15 ml) and extracted with Et_2O (3 x 20 ml). The dried (Na_2SO_4) Et_2O extract was evaporated to afford the diol 8 (67 mg, 85%) as a thick liquid bp 105-108°C (bath temp) at 0.2 mm Hg; ν_{max} (neat) 3340cm^{-1}; ^{1}H NMR δ 0.83 (3H, s, CH_3), 1.21 (3H, s, CH_3), 3.28 (δ_A) and 3.55 (δ_B) (2H, ABq, J = 10 Hz, CH_2OH), 4.96 (2H, brs, exchangeable with D_2O). Anal. calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found, C, 68.1; H, 11.36%.

(B) With Na-NH_3. To a well-stirred solution of 5 (77 mg, 0.5 mmol) in dry THF (5 ml) and dry redistilled NH_3 (50 ml), freshly scrapped Na (80.5 mg, 3.5 mg. atom) was added in portions during ca 5 min. After another 5 min the blue colour was discharged by dropwise addition of EtOH (ca 1 ml). After evaporation of NH_3 the residue was diluted with H_2O and extracted with Et_2O (3 x 20 ml). Evaporation of the dried (Na_2SO_4) extracts afforded the diol 8 (60 mg, 76%), identical (IR and ^{1}H NMR) with the sample described above.

(C) With $LiAlH_4$. A solution of the lactone 5 in dry Et_2O (15 ml) was added dropwise to a magnetically stirred suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in dry Et_2O (15 ml). The reaction mixture was refluxed for 1 h, cooled and the excess reagent was decomposed with ice-cold saturated Na_2SO_4 aq. Usual extraction with Et_2O followed by removal of solvent afforded the diol 8 (70 mg, 89%), identical (IR and ^{1}H NMR) with the samples described above.

Reduction of the Lactone 6. c-3-Hydroxymethyl-1-t-3,t-5-trimethyl-r-1-cyclohexanol (9). (A) Reduction of 6 (84 mg, 0.5 mmol) with Li-NH_3 as described for 5 afforded the diol 9 (71 mg, 83%), mp 93°C (Et_2O-light petroleum); ν_{max} (KBr) 3340cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 0.87 (3H, s, CH_3), 0.88 (3H, d, J = 6 Hz, $CHCH_3$) 1.23 (3H, s, CH_3), 1.4-2.0 (7H, m), 3.34 (δ_A) and 3.63 (δ_B) (2H, ABq, J = 10 Hz, CH_2OH) and 4.52 (2H, brs, $-CH_2OH$ and OH, exchangeable with D_2O). Anal. calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found : C, 69.5, H, 11.4%.

(B) Reduction of 6 (84 mg, 0.5 mmol) with Na-NH_3 as described for 5 gave 9 (65 mg, 76%), identical (IR and ^{1}H NMR) with the sample described above.

(C) Reduction of 6 (84 mg, 0.5 mmol) with $LiAlH_4$-Et_2O as described for 5 afforded 9 (73 mg, 85%), identical with the samples described above.

Reduction of the Lactone 7 : c-2-Benzyl-t-3-dimethyl-c-3-hydroxymethyl-r-1-cyclohexanol (10). (A) The reduction of 7 (122 mg, 0.5 mmol) with Li-NH_3 as described for 5 afforded a solid which was crystallised once from light petroleum-Et_2O to afford the diol 10 (102 mg, 82%), mp 157°C; ν_{max} (KBr) 3150 and 1600cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 0.85 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.20-2.43 (7H, m), 2.76-3.06 (2H, m, $ArCH_2$), 3.28 (δ_A) and 3.81 (δ_B) (2H, AB_q, J = 10 Hz, CH_2OH), 4.60 (2H, brs, exchangeable with D_2O, CH_2OH and OH) and 7.23 (5H, brs, ArH). Anal. calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found : C, 77.5; H, 9.7%.

(B) The reduction of 7 (122 mg, 0.5 mmol) with Na-NH_3 as described for 5 gave the diol 10 (86 mg, 69%), mp 157°C, identical (mixed mp and IR) with the sample described above.

(C) With $LiAlH_4$. The lactone 7 (122 mg, 0.5 mmol) in Et_2O (25 ml) was reduced with $LiAlH_4$ (76mg) as described for 5 to afford the diol 10 (105 mg, 85%), mp 157°C (light petroleum-Et_2O), identical (mixed mp and IR) with the samples described above.

Reduction of the Lactone (7) to c-3-Hydroxy-c-2-benzyl-1-t-3-dimethylcyclohexane-r-1-aldehyde (1→3) Hemiacetal (17)[9]. To a stirred solution of 7 (300 mg, 1.23 mmol) in dry Et_2O (20 ml) at 0°C under N_2 atmosphere was added DIBAL (ca 3 mmol). The reaction mixture was allowed to stir in the cold for 1 h and then hydrolysed by addition of saturated NH_4Cl aq. The Et_2O layer was separated and washed once with H_2O and dried (Na_2SO_4). After evaporation the hemiacetal 17 (276 mg, 91%) was obtained as a thick colourless liquid; ν_{max} (neat) 3380, 3020 and 1600cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 1.01 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.28-2.4 (7H, m) 2.64-3.08 (2H, m, $ArCH_2$), 3.37 (1H, brs, $CHOH$, exchangeable with D_2O), 5.32 (1H, s, -CHOH) and 7.0-7.48 (5H, m, ArH). Anal. calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.0. Found : C, 78.3; H, 9.1%.

Li-NH_3 Reduction of the Hemiacetal (17) to the Diol (10). The reduction of 17 (123 mg, 0.5 mmol) with Li-NH_3 as described for 5 gave the diol (10) (101 mg, 81%), mp 157°C, identical (mixed mp and IR) with the sample described above.

Reduction of the Lactone 11 to c-3-Hydroxy-t-2-benzyl-1-t-3-dimethylcyclohexane-r-1-aldehyde (1→3) Hemiacetal (13). (A) With Li-NH_3. The reduction of 11 (122 mg, 0.5 mmol) with Li-NH_3 as described for 5 afforded the hemiacetal 13 (110 mg, 89%), mp 100°C (light petroleum-Et_2O), ν_{max} (KBr) 3360 and 1600cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.16-1.70 (5H, m), 1.96-2.33

(2H, m), 2.4-2.75 (2H, m, $ArCH_2$), 3.95 (1H, brs, exchangeable with D_2O, CHOH), 4.96 (1H, s, CHOH) and 7.21 (5H, brs, ArH). Anal. calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.0. Found : C, 77.7; H, 8.8%.

(B) With $Na-NH_3$. The reduction of 11 (122 mg, 0.5 mmol) with $Na-NH_3$ as described for 5 gave 13 (87 mg, 71%), mp 100°C, identical (mixed mp, IR and ^1H NMR) with the sample described above.

t-2-Benzyl-1-t-3-dimethyl-c-3-hydroxymethyl-r-1-cyclohexanol (16). (A) Reduction of the Lactone 11. The reduction of 11 (122 mg, 0.5 mmol) in Et_2O with $LiAlH_4$ following the method as described for 5 gave the diol 16 (110 mg, 89%), mp 120°C (light petroleum-Et_2O); ν_{max} (KBr) 3330 (br) and 1600cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.36-3.06 (11H, m, 2H exchangeable with D_2O, methylene, methine, CH_2OH and OH), 2.95 (δ_A) and 3.15 (δ_B) (2H, AB_q, J = 10 Hz, CH_2OH) and 6.93-7.46 (5H, m, ArH). Anal. calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found : C, 77.6; H, 9.7%.

(B) Reduction of the Hemiacetal 13. The reduction of 13 (123 mg, 0.5 mmol) in dry Et_2O (25 ml) and $LiAlH_4$ (38 mg, 1 mmol) as described for 5 afforded 16 (117 mg, 95%), mp 120°C, identical (mixed mp, IR and ^1H NMR) with the sample described above.

Reduction of Lactone 14 : c-3-Hydroxy-t-2-Carbomethoxymethyl-1-t-3-dimethylcyclohexane-r-1-aldehyde (1→3) Hemiacetal (15). The reduction of 14 (106 mg, 0.5 mmol) in Et_2O with $Li-NH_3$ as described for 5 afforded the hemiacetal-acid 14 (91 mg, 85%); ν_{max} 3420 and 1710cm^{-1}. This was directly esterified with CH_2N_2 in Et_2O to the methyl ester 15, bp 120°C (bath temp.) at 0.1 mm Hg; ν_{max} 3420 and 1730cm^{-1}; ^1H NMR δ 0.86 (3H, s, CH_3), 1.16 (3H, s, CH_3), 2.21 (2H, brs, CH_2COOCH_3), 3.63 (3H, s, $COOCH_3$) and 4.83 (1H, brs, CH(OH)-O; the OH proton could not be located). Anal. calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found : C, 63.1; H, 8.8%.

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8. This is because the cyclic hemiacetal form engenders some flattering around the C-1,C-2,C-3 region which reduces van der Waals interactions due to the axial CH_2Ph group; in the ring-opened hydroxyaldehyde there is additional interaction between the axial CH_2Ph group and adjacent quaternary centres.

9. We thank Dr. J.S. Yadav of RRL, Hyderabad for this reaction.