reaction mixture was kept at 50 °C for 10 min, then cooled to room temperature and diluted with 50 mL of methanol to give a crystalline, light pink precipitate (1.6 g). It was dissolved in methylene chloride and treated with activated charcoal to give, after precipitation with methanol, 1.38 g (65%) of colorless crystals, identical in every respect with dimethyllepidopterene described previously.[2]

Oxidation of Lepidopterene. 10-(9-Anthrylmethyl)anthrone (6). A suspension of potassium permanganate (3.5 g) in acetone (100 mL) was added to a solution of lepidopterene (764 mg, 2 mmol) in methylene chloride (400 mL). The reaction mixture was then refluxed for 20 h, and during this period an additional 6 g of potassium permanganate was added in two portions. Workup by filtration and evaporation of solvent and treatment of the residue with methylene chloride (10 mL) gave 560 mg of insoluble lepidopterene. Column chromatography (silica gel/methylene chloride) of the filtrate gave an additional 130 mg of recovered lepidopterene and 50 mg of **6**. Pale green-yellow needle-shaped crystals, mp 191–194 °C, yield 66% (based on converted lepidopterene). M^+ found by high-resolution MS: 384.150. Calcd. for $C_{29}H_{20}O$: 384.151. MS fragmentation: 384 (0.5), 383 (0.6), 382 (2), 195 (4), 194 (32), 193 (15), 192 (37), 191 (100), 190 (11), 189 (27), 165 (42). IR (KBr): 1650 cm^{-1} (CO).

Registry No.—**1b** (X = I), 27998-91-0; **4a**, 55614-27-2; **7a**, 4709-80-2; **7b**, 68975-27-9; **7c**, 68975-28-0; **8**, 642-31-9.

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Factors Influencing Regioselectivity in Lithium Aluminum Hydride Reduction of Unsymmetrical Dicarboxylic Acids

Margaret M. Kayser and Peter Morand*

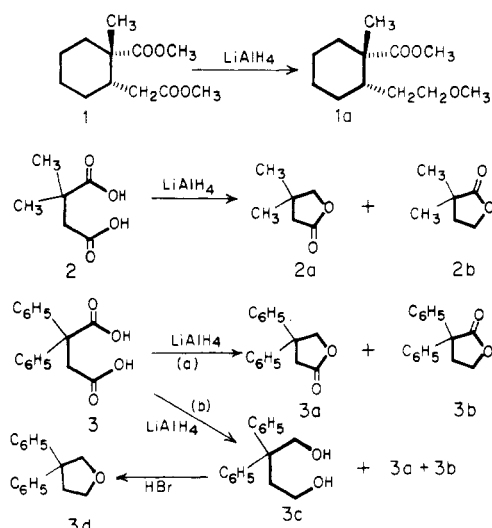*Department of Chemistry, University of Ottawa, Ottawa Canada K1N 9B4*

It has been demonstrated[1] that LiAlH$_4$ is an efficient reagent for the reduction of carboxylic acids to alcohols. However, selective reduction of one of two carboxylic acid groups in the same molecule is not easily achieved. Nystrom and Brown[2] reported failure in the selective reduction of sebacic acid. In the study of the reduction of camphoric and 1-ethyl-

1-butylglutaric acids Noyce and Denney[3] found that the former gave only the corresponding diol and recovered starting material whereas the latter yielded a mixture of original acid (14%), 2-ethyl-2-butyl-1,5-pentanediol (11%), and a lactone (40%) identified as 1-ethyl-1-butyl-γ-valerolactone. Similarly, the selective reduction of the *primary* carbomethoxy group (in 53% yield) of the dimethyl ester of *cis*-2-methyl-2-carboxycyclohexaneacetic acid (1) was reported by Bachmann and Dreiding.[4]

More recent work has shown that metal hydride reduction of unsymmetrical cyclic anhydrides[5] often yields lactones resulting from addition of hydride ion to the more sterically hindered carbonyl group. Preference for the more hindered carbonyl function is especially pronounced in cyclic anhydrides containing tertiary vs. primary carbonyl groups. Since these findings contrast with the results reported for the reduction of diacids and diester[3,4] it was decided to determine the degree of regioselectivity in the reductions of carboxylic diacids corresponding to some of the anhydrides already investigated. This paper describes the results obtained in the LiAlH$_4$ reduction of three dicarboxylic acids and a diester corresponding to one of the acids.

The reduction of diacids **2** and **3** yielded, apart from re-

covered starting material, mixtures of isomeric lactones. In both cases, the lactone obtained in major yield (see Table I) corresponded to reduction of the carboxyl group adjacent to the tertiary carbon atom. Under comparable reaction conditions diacid **4** was not reduced. Reduction of diester **5** proved to be the most regioselective, yielding only one reduction product, 2,2-dimethyl-γ-butyrolactone (**2a**). These results suggest that regioselective reduction of dicarboxylic acids does not have the same synthetic potential[6] as the corresponding cyclic anhydrides (see Table I). However, the ratio of lactones obtained in the reduction of the former is of considerable interest in view of the mechanism of nucleophilic addition to the carbonyl function.

Recent theoretical[7] and experimental[8] evidence points to a nonperpendicular approach in nucleophilic additions to a

Table I. Product Distribution in LiAlH$_4$ Reductions[a]

compd	LiAlH$_4$/ acid (ester)	total yield[b]	starting material[b]	lactonic product[b]	ratio of product (a:b)
2	1/2	84 (80)	58 (10)	26 (70)	2.3:1 (19:1)
3	1/2	81 (84)	41 (0)	40 (84)	2.5:1 (a only)
4	1/2	85 (75)	85 (0)	0 (75)	– (a only)
5	1/1.25	67 (80)	45 (10)	22 (70)	a only (19:1)

[a] Yields and ratios for corresponding anhydrides given in parentheses.[5] [b] In percent.

carbonyl group. Baldwin's modification[9] implies that the path of an incoming nucleophile may be further restricted when
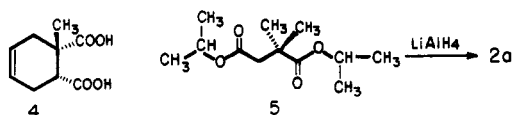
neighboring atoms such as N (amide function) or O (ester or carboxylic function) are present. We have suggested[5] that these steric restrictions should be considered in explaining the preferential reduction of the more sterically hindered carbonyl function in unsymmetrically substituted cyclic anhydrides. However, the results of metal hydride reductions of a number of cyclic anhydrides indicate that regioselectivity of these reactions might also be controlled by electronic factors. In cyclic anhydrides such as 2,2-dimethylsuccinic anhydride or 2,2-diphenylsuccinic anhydride both electronic and steric effects favor reduction of the more hindered carbonyl group. Since the approach vector for nucleophilic attack is directed toward the plane of the cyclic anhydride at an angle of ca. 110° and is shifted away from the ring oxygen, the nucleophilic path directed at the less hindered carbonyl group is blocked by β substituents (R in 6). Attack on the more sterically hindered

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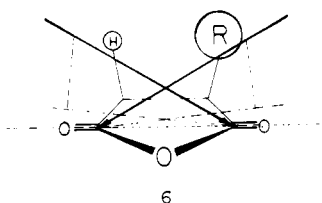
carbonyl group, on the other hand, is obstructed only by a hydrogen atom. At the same time the oxygen atom of the carbonyl group α to the tertiary carbon atom is more basic and therefore more apt to be associated with Li$^+$ cation. The catalytic role of this association in metal hydride reductions is well established.[10] As a result of these combined effects the reduction is highly regioselective.

Diacids 2 and 3 are capable of forming strong intramolecular hydrogen bonds. The hydrogen-bonded ring that might form would nevertheless be flexible and, consequently, the steric restrictions encountered by the nucleophile are more difficult to assess than those illustrated (6) for the flat and rigid anhydrides. Electronic factors, however, remain the same and are probably responsible for the preferential reduction of the carbonyl group adjacent to the tertiary carbon atom. Similarly, the primary carboxyl group in diester 5 appears to be sterically more accessible to nucleophilic attack than the tertiary group. Since the only reduction product observed is the lactone resulting from reduction of the more encumbered carboxyl function it appears that the site of reduction is fixed from the initial association of Li$^+$ cation with the more basic of the two oxygen atoms (of the carbonyl groups).

In conclusion, the results reported here suggest that electronic effects play an important role on regioselectivity in metal hydride reduction of carbonyl functions. This is especially evident in the reduction of diester 5 where electronic influences compete against steric hindrance. In this particular case the steric restrictions are not severe and the regioselectivity of the reaction is therefore governed by electronic factors.

Experimental Section

Tetrahydrofuran (THF) and diethyl ether were dried over LiAlH₄ and distilled under nitrogen.

Infrared spectra were recorded on a Beckman IR-20 instrument. The ¹H NMR spectra, in CDCl₃ with Me₄Si as internal standard, were obtained on a Varian T-60 or HA-100 instrument.

GLC analyses were carried out with an Autoprep Model A-700 gas chromatograph.

Reduction of 2,2-Dimethylsuccinic Acid 2 (Method A). A solution of 2,2-dimethylsuccinic acid (6.5 g; 0.045 mol) in anhydrous ether (200 mL) was added at −20 °C to a stirred solution of LiAlH₄ (0.95 g, 0.025 mol) in anhydrous ether (50 mL) over a period of 40 min. After being warmed to room temperature, the reaction mixture was cooled in an ice-bath and acidified with 6 N HCl. Stirring was continued until the reaction mixture became clear (1.5 h). The organic layer was separated and the aqueous layer extracted twice with ether. The combined organic layers were dried with anhydrous MgSO₄ and concentrated. The unreacted diacid (3.8 g) crystallized and was filtered. The remaining mixture was concentrated further to give an oily product (1.7 g). The GLC and ¹H NMR analyses showed a mixture of two lactones: β,β-dimethyl-γ-butyrolactone (2a) and α,α-dimethyl-γ-butyrolactone (2b) in a ratio of 2.3:1; ν_{max} 1775 cm⁻¹ (lactone). Using Method B described below, the same ratio of lactones was obtained.

Reduction of 2,2-Diphenylsuccinic Acid 3 (Method B). (a) A solution of 2,2-diphenylsuccinic acid (2.7 g, 0.01 mol) in dry THF (50 mL) was added at −15 °C to a stirred solution of LiAlH₄ (0.19 g, 0.005 mol) in THF (25 mL). The reaction mixture was warmed to room temperature over a period of 4 h. After cooling in an ice-bath the reaction mixture was acidified with 6 N HCl. The organic layer was separated and the aqueous layer extracted twice with ether. The combined organic layers were dried over anhydrous MgSO₄ and concentrated. The oil obtained (2.18 g, 81%) was analyzed by ¹H NMR. The mixture consisted of 50% lactonic product and 50% unreacted acid. The acid was removed by extraction with saturated NaHCO₃ solution. The remaining lactones were found to be present in a ratio of 2.5:1 in favor of β,β-diphenyl-γ-butyrolactone (3a). (b) Overnight reduction at room temperature yielded crude diol, 3c. The diol was cyclized by warming with HBr. The product, analyzed by ¹H NMR, showed a mixture of 80% ether 3d and 20% of the lactonic material with β,β-diphenyl-γ-butyrolactone (3a) being more abundant (2:1); ν_{max} 1780 cm⁻¹ (lactone).

Reduction of cis-1-Methylcyclohex-4-ene-1,2-dicarboxylic Acid (4). The reduction of 4 according to methods A and B yielded only crude starting material on usual workup.

Reduction of Diisopropyl Ester of 2,2-Dimethylsuccinic Acid 5. The diester 5 (1.4 g, 0.006 mol) dissolved in dry THF (20 mL) was cooled and added dropwise to a stirred solution of LiAlH₄ (0.19 g; 0.005 mol) in THF (10 mL) cooled in a dry-ice–acetone bath. The reaction mixture was stirred for 4.5 h at −15 °C, then quenched with distilled water, and acidified with 6 N HCl. The reaction mixture was worked up in the usual manner to give an oil (0.99 g). The reduction product was analyzed by GLC and ¹H NMR. The mixture consisted of 2,2-dimethyl-γ-butyrolactone (2a) (22%) and unreacted diester 5 (45%); ν_{max} 1775 cm⁻¹ (lactone).

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