enetetrahydropyran, and 2,4,6-trimethyltetrahydropyran-4-ol. It is suggested that the formation of the two pyrans during the dehydration of 2-methyl-2,4-pentanediol occurs principally by a similar reaction.

2. The reaction of other aldehydes and of ketones with 4-methyl-4-penten-2-ol has given products which are believed to be analogous to those obtained by the similar reaction of acetaldehyde.

EMERYVILLE 8, CALIFORNIA RECEIVED MAY 8, 1950

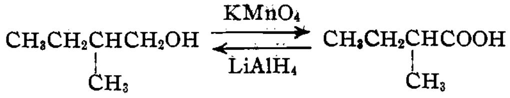
[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA]

Steric Effects and Stereochemistry of Lithium Aluminum Hydride Reduction

BY DONALD S. NOYCE AND DONALD B. DENNEY

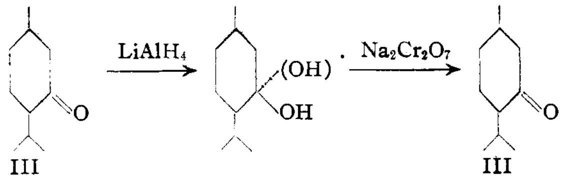
The versatility of reduction with lithium aluminum hydride[1] has prompted a study of the applicability of this reagent to selective reduction. Three different types of reduction have been explored in the present investigation: reduction next to a racemizable asymmetric center, selective reduction of one of two like functional groups, and reduction to introduce a new center of asymmetry, to determine the suitability of this reagent for preparation of one isomer in preponderance over the alternate isomer.

Reduction of the first type shows clean-cut results. When 2-methylbutanoic acid (I) (prepared by the oxidation of 2-methyl-1-butanol (II)) was reduced, II of unchanged rotation was obtained in 83% yield. Further, when *l*-menthone (III) was reduced, a mixture of menthols was obtained which was reoxidized to *l*-menthone with insignificant change of rotation.



$$CH_3CH_2\underset{CH_3}{\underset{|}{C}}HCH_2OH \underset{LiAlH_4}{\overset{KMnO_4}{\rightleftarrows}} CH_3CH_2\underset{CH_3}{\underset{|}{C}}HCOOH$$

II $[\alpha]^{23}D$ −4.98°, −5.03° I



III $[\alpha]^{25}D$ −25.20° $[\alpha]^{25}D$ −28.00° III $[\alpha]^{26}D$ −24.70°

These results show clearly that an asymmetric center next to a carboxyl or carbonyl is unaffected by reduction. Similar results have been reported previously, but only in instances where additional centers of asymmetry complicated the simple clarity of the results.[2]

Selective reduction of one of two like functional groups does not proceed cleanly, as previous results might lead one to expect. Nystrom and Brown[3] reported failure in selective reduction of sebacic acid. The highly hindered carboxyl group of podocarpic acid has been reduced under conditions somewhat more drastic than usual,[4] and Bachmann and Dreiding[5] have recently reported an unsymmetrically substituted diester to give 53% of crude hydroxy ester. On the other hand, an amido acid has been reported to be reduced only at the free carboxyl group.[6] Two acids were investigated, camphoric acid and α-ethyl-α-butylglutaric acid (IV). Camphoric acid gave poorly defined results, large amounts of diol and recovered acid being the main products of reduction. Inverse addition of one mole of lithium aluminum hydride to IV gave 39% of the theoretical amount of α-ethyl-α-butyl-δ-valerolactone (V), 14% recovered acid and 11% crude 2-ethyl-2-butyl-1,5-pentandiol (VI). This contrasts with the observation that esterification of IV gives only α-ethyl-α-butyl-γ-carbomethoxybutyric acid,[7] with no detectable amounts of its isomer. In these cases there are undoubtedly better ways to accomplish the same results, and hence there appears to be no advantage to lithium aluminum hydride for this type reduction.

More interesting results were obtained in the investigation of the introduction of a new center of asymmetry. The results are summarized in Table I.

TABLE I

Compound reduced	LiAlH$_4$	*cis* product, % Al(O-*i*-Pr)$_3$	H$_2$(Pt)	Method of analysis, present work
4-Methylcyclohexanone	19	33[8]		Density
3-Methylcyclohexanone	8	55[8](30[9])		Density
2-Methylcyclohexanone	36	58(50,[8] 6–14[10])	75[12]	Density
l-Menthone	29	70[11]	"Mainly"[13]	Opt. rot.
d-Camphor	90	70[8]	90[14]	Opt. rot.

Trevoy and Brown[15] have shown that lithium aluminum hydride opens oxide rings by a bimolecular inversion mechanism, and it seemed likely that similar addition of hydrogen to a carbonyl group

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[1] (a) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947); (b) Karrer, Portman and Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

[2] Fieser, Fieser and Chakravarti, THIS JOURNAL, **71**, 2226 (1949); Stoll, Hofman and Schleintz, *Helv. Chim. Acta*, **32**, 1947 (1949).

[3] Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1947).

[4] Zeiss, Slimowicz and Pasternak, *ibid.*, **70**, 1981 (1948).

[5] Bachmann and Dreiding, *ibid.*, **71**, 3222 (1949).

[6] Karrer, Suter and Waser, *Helv. Chim. Acta*, **32**, 1937 (1949).

[7] Cason, *J. Org. Chem.*, **13**, 227 (1948).

[8] Jackman, Macbeth and Mills, *J. Chem. Soc.*, 2641 (1949).

[9] Mousseron, Marszak and Bolle, *Bull. soc. chim.*, **9**, 260 (1942).

[10] Anziani and Cornubert, *ibid.*, **12**, 359 (1945).

[11] Zeitschel and Schmidt, *Ber.*, **59**, 2303 (1926); also ref. 8.

[12] Skita and Faust, *ibid.*, **64**, 2878 (1931).

[13] Vavon and Couderc, *Compt. rend.*, **179**, 405 (1924).

[14] Vavon and Peignier, *ibid.*, **181**, 183 (1925).

[15] Trevoy and Brown, THIS JOURNAL, **71**, 1675 (1949).

should also occur from the side opposite a hindering group to give a product with the hydroxyl group in the "*cis*" position. Previously reported examples[16] agree with this picture and, as mentioned by Bachmann,[16b] catalytic hydrogenation, lithium aluminum hydride reduction and Meerwein–Ponndorf–Verley reduction often lead to a preponderance of the same isomer.

The results here reported serve to qualify this picture. Considering the series of methylcyclohexanones, the proportion of *cis* epimer is not as great as in reduction with aluminum isopropoxide,[8] which is probably due to the smaller steric requirements of the reducing step of the reaction (which may be hydrogen donation by an incipient AlH_4^- ion,[15] or in subsequent stages of the reaction by hydrogen migration in a ketone $Al \cdot H_3$ complex).[17]

Even in the case of *l*-menthone, the steric effects are not sufficient to produce a large amount of *cis* product (neomenthol) whereas both catalytic hydrogenation and aluminum isopropoxide reduction afford a marked preponderance of *cis* isomer.

Finally, when steric hindrance is sufficiently great, clean predominance of addition of hydrogen from the unhindered side does occur, as in the case of camphor. Thus predominance of the *cis* isomer requires a marked steric hindrance for attack to occur largely on one side of the molecule. The cases reported by Shoppee and Summers and Bachmann and Dreiding[16] agree with this generalization. A further consequence, however, is that where the isomer of opposite configuration than that obtained by catalytic hydrogenation is desired, lithium aluminum hydride may offer an advantage.

Experimental[18]

Preparation and Reduction of (+)-2-Methylbutanoic Acid (I).—To a solution of 52 g. (0.33 mole) of potassium permanganate and 4 g. (0.1 mole) of sodium hydroxide in one liter of water 20 g. (0.225 mole) of 2-methyl-1-butanol $[\alpha]^{23}D$ −4.98° (homog.)[19] was added. After 2.5 hours at room temperature, the mixture was extracted with ether, acidified and extracted with three portions of ether. The ether solution of I was dried over magnesium sulfate and fractionated to give I, b. p. 172–174°, 12 g. (52%), $[\alpha]^{22}D$ 17.10° (homog.).

A solution of 11 g. (0.11 mole) of I in 200 ml. of anhydrous ether was added over a period of one-half hour to a stirred suspension of 5.5 g. (80% excess) of lithium aluminum hydride in 200 ml. of anhydrous ether. The mixture was allowed to stir 15 minutes longer, then the excess lithium aluminum hydride was destroyed by the addition of water and dilute sulfuric acid. The ether layer was washed with 1 *N* sodium carbonate, dried and distilled to give 7.8 g. (83%) of 2-methyl-1-butanol (II), b. p. 128.0–128.5°, $[\alpha]^{23}D$ −5.03° (homog.).

Reduction of Methylcyclohexanones.—The three starting ketones had the following properties: 2-methylcyclohexanone distilled through an 18″ modified Podbielniak column, b. p. 89° (77 mm.), $n^{25}D$ 1.4462; 3-methylcyclohexanone, prepared by the oxidation of 3-methylcyclohexanol[20] and purified over the sodium bisulfite addition product, b. p. 62–63° (17 mm.), $n^{25.5}D$ 1.4438; 4-methylcyclohexanone, $n^{25}D$ 1.4428.

To a refluxing mixture of 6.25 g. (0.165 mole) of lithium aluminum hydride and 200 ml. of anhydrous ether 18.25 g. (0.163 mole) of 3-methylcyclohexanone dissolved in 50 ml. of anhydrous ether was added at such a rate as to keep the mixture gently refluxing. The mixture was heated under reflux for an additional 6 hours, excess lithium aluminum hydride was destroyed by the addition of ice and 6 *N* hydrochloric acid and the layers separated. The ether layer was washed with 1 *N* sodium carbonate, dried over sodium sulfate and distilled to afford 16.25 g. (88%) of a mixture of *cis* and *trans* 3-methylcyclohexanol, b. p. 91–93° (42 mm.), $n^{22}D$ 1.4560, d^{30}_4 0.9077 (corresponding to 8% *cis*-3-methylcyclohexanol in the mixture[21]).

Prepared in similar manner, 2-methylcyclohexanol, b. p. 92–93° (55 mm.), $n^{22}D$ 1.4626, d^{30}_4 0.9210 (corresponding to 36% *cis*-2-methylcyclohexanol in the mixture[22]); 4-methylcyclohexanol, b. p. 89–91° (40 mm.), $n^{22}D$ 1.4560, d^{30}_4 0.9065 (corresponding to 19% *cis*-4-methylcyclohexanol in the mixture[22]).

Meerwein–Pondorff–Verley Reduction of 2-Methylcyclohexanone.[23]—A solution of 15.4 g. (0.075 mole) of aluminum isopropoxide dissolved in 220 ml. of dry isopropyl alcohol was placed in 500-ml. 3-necked flask, equipped with a thermometer, dropping funnel and 35-plate column. To the refluxing solution 25 g. (0.22 mole) of 2-methylcyclohexanone in 25 ml. of dry isopropyl alcohol was added over a period of 5 minutes. The head temperature of the column dropped to 59° in 10 minutes, then rose to 82.5° in 2.5 hours at which time no test for acetone could be obtained. As the isopropyl alcohol and acetone were distilled from the mixture, more dry isopropyl alcohol was added, a total of 75 ml. of distillate being taken. Most of the remaining isopropyl alcohol was distilled from the reaction mixture at atmospheric pressure, then the solution was cooled, hydrolyzed with dilute hydrochloric acid and extracted with three 100-ml. portions of ether. The ether solution was washed with water and dried over magnesium sulfate. Distillation afforded 21.5 g. (85%) of 2-methylcyclohexanol, b. p. 89–90° (52 mm.), $n^{21}D$ 1.4638, d^{30}_4 0.9232 (corresponding to 58% *cis*-2-methylcyclohexanol in the mixture[22]).

Partial Inversion of *cis*-2-Methylcyclohexanol.—When 10 g. (0.09 mole) of the above *cis*-rich mixture was heated under reflux with 6.2 g. (0.03 mole) of aluminum isopropoxide in 100 ml. of isopropyl alcohol with the addition of 0.4 ml. (6 mole %) of acetone for 3 hours the resulting product had b. p. 90° (52 mm.), d^{30}_4 0.9198 (corresponding to 24% *cis*-2-methylcyclohexanol in the mixture[22]).

Reduction of *l*-Menthone (III).—*l*-Menthone (III) was prepared by the oxidation of *l*-menthol,[20] b. p. 96.5–97.5° (21 mm.), $[\alpha]^{25}D$ −25.20° (homog.).

To a stirred refluxing solution of 6.30 g. (0.166 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether, 17.93 g. (0.116 mole) of III in 50 ml. of anhydrous ether was added over a period of one-half hour, and allowed to reflux an additional 10 hours. Excess lithium aluminum hydride was decomposed, the ether layer separated, and

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(16) (a) Shoppee and Summers, *J. Chem. Soc.*, 687 (1950); (b) Bachmann and Dreiding, This Journal, **72**, 1323 (1950).

(17) "Random reduction" which one might therefore expect to occur in the cases of 3-methylcyclohexanone and 4-methylcyclohexanone does not necessarily lead to formation of equal amounts of the two isomers. In so far as the activated complex partakes of the character of the product, the more stable isomer will predominate, here the *trans* isomer.

(18) Analyses are by the Microanalytical Laboratory of the University of California. Melting points are corrected, boiling points uncorrected.

(19) We wish to express our appreciation to Prof. W. E. Doering for a generous supply of active amyl alcohol. He informs us that the sample nsed was over 95% pure, though approximately 15% racemized (See Thesis, T. C. Aschner, Columbia University, 1947).

(20) "Organic Syntheses," Coll. Vol. I, p. 340.

(21) Macbeth and Mills, *J. Chem. Soc.*, 709 (1945), report the properties of the pure isomers.

(22) Jackman, Macbeth and Mills, *ibid.*, 1717 (1949).

(23) In view of the well-known equilibrium nature of the Meerwein-Pondorff-Verley reaction [Linstead, *Ann. Repts. Chem. Soc.* (*London*), **34**, 230 (1937); Doering and Young, This Journal, **72**, 631 (1950)] the reduction of 2-methylcyclohexanone was reinvestigated, taking into consideration the conditions which would reduce as largely as possible the equilibration.

the aqueous layer extracted with two 25-ml. portions of ether. The combined ether extracts were washed with 1 *N* sodium carbonate, and dried over anhydrous sodium sulfate. Removal of the ether afforded 16.25 g. (90%) of a mixture of menthol and neomenthol, $[\alpha]^{25}$D −28.00° (homog.) (corresponding to 71% *l*-menthol in the mixture[24]). Variation in the molar excess of lithium aluminum hydride produced no appreciable change in the composition of the product. When 10 g. of the above mixture was reoxidized to menthone, 7.0 g. (71%) of III, $[\alpha]^{26}$D −24.70° (homog.) was obtained.

Reduction of *d*-Camphor.—*d*-Camphor[25] was recrystallized from ethanol, m. p., 177–178°, $[\alpha]^{25}$D 42.8° (*c* 10 in ethanol).

A solution of 15 g. (0.099 mole) of camphor in 50 ml. of anhydrous ether was added over a period of 1 hour to a stirred refluxing suspension of 4.5 g. (0.119 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether. The mixture was allowed to reflux 12 hours to ensure complete reduction, and the excess lithium aluminum hydride dedecomposed with water and 6 *N* hydrochloric acid. The ether layer, dried over sodium sulfate was carefully evaporated to give a mixture of borneol and isoborneol, which was air-dried; 14.10 g. (94%), $[\alpha]^{25}$D −26.00° (*c* 10 in ethanol).[26]

Reduction of α-Ethyl-α-butylglutaric Acid (IV).—A solution of 1.8 g. (0.047 mole) of lithium aluminum hydride in 55 ml. of anhydrous ether was added at −15° to 9.18 g. (0.043 mole) of IV dissolved in 200 ml. of anhydrous ether over a period of 40 minutes. After allowing to warm to room temperature, ice and 6 *N* hydrochloric acid were added to decompose any unreacted lithium aluminum hydride and the reduction complex. The separated ether layer was extracted with four 25-ml. portions of 2 *N* sodium hydroxide and concentrated to give 0.88 g. (11%) of crude 2-ethyl-2-butyl-1,5-pentandiol (see below).

Extraction of the acidified sodium hydroxide extracts gave a mixture of recovered IV and α-ethyl-α-butyl-δ-valerolactone, which was further separated by extraction with 1 *N* sodium carbonate solution. In this manner there was obtained 1.30 g. (14%) recovered IV, m. p. 77–80°.

The ether solution of the lactone, dried over sodium sulfate, was fractionated, b. p. 114–115° (4.5 mm.), to give 3.06 g. (39%), d^{25}_{4} 0.9699, n^{25}D 1.4620, *M*D calcd. 52.3, found 52.2. There was a residue of 0.75 g. (10%) from the distillation.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.74; H, 10.87. Found: C, 72.03; H, 11.01.

Preparation of 2-Ethyl-2-butyl-1,5-pentanediol.—A solution of 10 g. (0.046 mole) of IV in 50 ml. of ether was added slowly to a stirred refluxing suspension of 7.92 g. (0.21 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether. After refluxing overnight, excess lithium aluminum hydride was decomposed with ice and 6 *N* hydrochloric acid. The separated ether layer was washed with 1 *N* sodium carbonate, dried over sodium sulfate, and fractionated. In this manner there was obtained 6.54 g. (75%) of 2-ethyl-2-butyl-1,5-pentanediol, b. p. 146° (4 mm.), n^{24}D 1.4671, d^{25}_{4} 0.9414.

Anal. Calcd. for $C_{11}H_{24}O_2$: C, 70.20; H, 12.78. Found: C, 70.12; H, 12.80.

The bis-(3,5-dinitrobenzoate) was prepared in the usual manner.[27] Recrystallized three times from ethanol, m. p. 98.2–98.7°.

Anal. Calcd. for $C_{25}H_{28}N_4O_{12}$: C, 52.08; H, 4.90; N, 9.72. Found: C, 52.08; H, 5.11; N, 9.93.

Summary

Selective reduction with lithium aluminum hydride has been shown to be generally only slightly affected by steric effects. It has also been shown that lithium aluminum hydride does not affect racemizable asymmetric centers.

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(24) Simonsen, "The Terpenes," Cambridge Univ. Press, p. 243, lists the properties of the pure isomers.

(25) Purchased from Magnus, Mabee and Reynard, New York.

(26) Hückel, *Ann.*, **549**, 183 (1941), reports that the rotation of both borneol and isoborneol are independent of concentration in ethanol. The result above therefore indicated the formation of 90% isoborneol and 10% borneol.

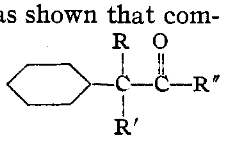
(27) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., p. 138.

BERKELEY 4, CALIFORNIA RECEIVED JUNE 5, 1950

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Dipole Moments of Some α-Phenyl Ketones[1]

BY EDWARD L. ALPEN[2] AND W. D. KUMLER

In the previous papers[3,4] it was shown that compounds of the general type 

where the R's can be aliphatic, aromatic or hydrogen, have a band of abnormally high extinction in the region 270–320 mμ, which was interpreted as arising from an interaction between the carbonyl and the phenyl groups. The interaction was considered both as a quantum mechanical perturbation and a no-bond resonance phenomenon. This investigation of the same compounds was undertaken to see whether or not the electronic interactions giving rise to the spectral anomalies also resulted in abnormal dipole moment values.

Measurements of the dipole moments were made in benzene solution at 30°. The moments were calculated by the method of Halverstadt and Kumler[5] using the equations

$$p_{2_0} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\frac{\epsilon_1 - 1}{\epsilon_1 + 2}$$

$$P_{2_0} = p_{2_0}\mathrm{M} \quad \mu = 0.01281\sqrt{(P_{2_0} - P_{\mathrm{E}_2})T}$$

and the graphical modification for obtaining ϵ_1, v_1, α and β. In Figs. 1 and 2 it is seen that the ϵ_{12}–ω_2 curves are linear in all cases. P_{E_2} values were calculated using the group refractions given by

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(1) Abstracted in part from the dissertation presented by E. L. Alpen in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Chemistry.

(2) Fellow American Foundation for Pharmaceutical Education, 1949. Department of Pharmacology, The George Washington University School of Medicine, Washington 5, D. C.

(3) Kumler, Strait and Alpen, THIS JOURNAL, **72**, 1463 (1950).

(4) Alpen, Kumler and Strait, *ibid.*, **72**, 4558 (1950).

(5) Halverstadt and Kumler, *ibid.*, **64**, 2988 (1942).