cis-3-Bromo-2-propen-1-ol: 3.00, 3.46, 6.21, 6.98, 7.77, 8.25, 8.58, 9.75, 10.4, 13.8.

trans-3-Bromo-2-propen-1-ol: 3.00, 3.46, 6.26, 7.05, 7.40, 7.80, 8.10, 8.46, 9.28, 9.60, 9.88, 10.39, 10.8, 13.0, 13.9.

cis-1-Bromo-3-chloro-1-propene: 6.35, 7.13, 7.77, 8.16, 8.86, 9.89, 10.9, 13.2, 14.5.

trans-1-Bromo-3-chloro-1-propene: 6.37, 7.13, 7.94, 8.10, 8.35, 8.57, 9.52, 10.18, 10.7, 11.1, 12.68, 13.27, 13.83, 14.2, 14.8.

Reaction with Potassium Iodide in Acetone at 20°.—The usual procedure[10] was modified to permit rapid handling of the samples and minimum exposure to light. The samples were mixtures of known composition of the two isomers. The compounds were transferred and weighed in a 1-ml. hypodermic syringe and the weight of sample was determined by difference. Both the allylic chloride and the potassium iodide solutions were brought to thermal equilibrium then combined, in the dark, and samples were taken at the desired time interval.

The usual modified second-order equation, $k = 2.303/4bt \log_{10} (5 - z/5(b - z)$, was used, and a plot of $\log_{10} (5 - z/5 (1 - z)$ *vs.* time gave a straight line between 35 and 74% reacted for *cis*-1-bromo-3-chloro-1-propene (95%) and between 50 and 82% reacted for *trans*-1-bromo-3-chloro-1-propene (75%). The k values thus obtained were plotted against composition and the k value for each pure isomer determined by extrapolation.

A mixture of the 1-bromo-1-propenes did not react with potassium iodide in acetone at 20° in six hours.

Reaction with Sodium Ethoxide in Ethanol at 50°.—The usual procedure[11] was modified in a manner similar to that used with potassium iodide and for the same reason. The data were calculated using the rate expression for a second-order reaction. The sodium ethoxide solution was 0.04996 M for the reaction with *cis*-1-bromo-3-chloro-1-propene (95%) (0.04518 M) and 0.04969 M for the reaction with *trans*-1-bromo-3-chloro-1-propene (74%) (0.05367 M). A plot of $\log_{10} b(a - x)/a(b - x)$ *vs.* time gave a straight line between 13 and 65% reacted for *cis*-1-bromo-3-chloro-1-propene and between 19 and 70% reacted for *trans*-1-bromo-3-chloro-1-propene.

1-Bromo-1-propene was treated in a similar manner with sodium ethoxide and reacted to the extent of 1% in two hours, 4% in six hours and 10% in 18 hours. The data obtained for the 1-bromo-3-chloro-1-propenes were corrected for the extent of reaction of the vinyl bromine atom. The k values for the pure samples were obtained by extrapolation.

AUSTIN, TEXAS

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[10] L. F. Hatch, L. B. Gordon and J. J. Russ, THIS JOURNAL, **70**, 1093 (1948).

[11] L. F. Hatch and H. E. Alexander, *ibid.*, **71**, 1037 (1949).

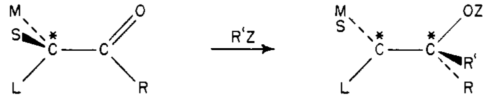
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Studies in Stereochemistry. XX. Steric Control of Asymmetric Induction in the Preparation of the 3-Cyclohexyl-2-butanol System[1]

BY DONALD J. CRAM AND FREDERICK D. GREENE

RECEIVED JULY 16, 1953

The applicability of the "Rule of Steric Control of Asymmetric Induction" to reactions producing diastereomeric mixtures of 3-cyclohexyl-2-butanol has been studied. The reactions of methylmagnesium iodide, methyllithium in ether and methyllithium in pentane with 2-cyclohexylpropanal, and of lithium aluminum hydride and sodium borohydride with 3-cyclohexyl-2-butanone were found to give product balances qualitatively predicted by the rule. The reversible reaction of aluminum isopropoxide with 3-cyclohexyl-2-butanone gave results at variance with the rule, even though the product balance was kinetically controlled.



L > M > S in effective bulk

In previous papers in this series[2] an empirical rule has been developed to correlate and predict the stereochemical direction of asymmetric induction in reactions of acyclic systems in which a new asymmetric center is created adjacent to an old. "In non-catalytic reactions of the type shown (formulas), that diastereomer will predominate which would be formed by the approach of the entering group from the *least* hindered side of the double bond when the rotational conformation of the C–C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric center." A total of 14 syntheses where L, M and S are aryl, alkyl or hydrogen are now known which are consistent with the rule, and 18 well-authenticated syntheses[3] in which M is an amino, hydroxyl or methoxy group have been found[4] to correlate with the generalization. The steric course of 12 other syntheses which are somewhat more ambiguous also appears to be consistent with the correlation.[2] The current investigation was undertaken to determine further the scope and limitations of this rule, and to attempt to discover the rationale underlying its operation.[5]

The reactions of 2-cyclohexylpropanal (I) and 3-cyclohexyl-2-butanone (II) which lead to mixtures of diastereomers of 3-cyclohexyl-2-butanol (III) were chosen for two reasons. (1) The asymmetric carbon atom of the two starting materials (I and II) carries *fully saturated groups* of widely differing bulk which are incapable of becoming involved in other than a steric sense in the transition states of the reactions in question. (2)

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[1] This work was generously supported by the Office of Ordnance Research, U. S. Army.

[2] (a) D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 5828 (1952); (b) D. J. Cram and J. D. Knight, *ibid.*, **74**, 5835, 5839 (1952); (c) D. J. Cram, F. A. Abd Elhafez and H. Weingarten, *ibid.*, **75**, 2293 (1953).

[3] The configurations of the predominant product are well established, and the reactions are non-reversible (this excepts those reactions involving aluminum isopropoxide as a reducing agent for a ketone).

[4] D. Y. Curtin and E. K. Meislich, *ibid.*, **74**, 2901 (1952).

[5] Since our original correlation appeared (ref. 2a), V. Prelog [*Helv. Chim. Acta*, **36**, 308 (1953); see also V. Prelog and H. L. Meyer, *ibid.*, **36**, 320 (1953), and W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *ibid.*, **36**, 325 (1953)] published an extension and an interpretation of the observations of McKenzie and co-worker (see above for references) regarding the steric course of addition reactions to menthyl pyruvate and similar compounds.

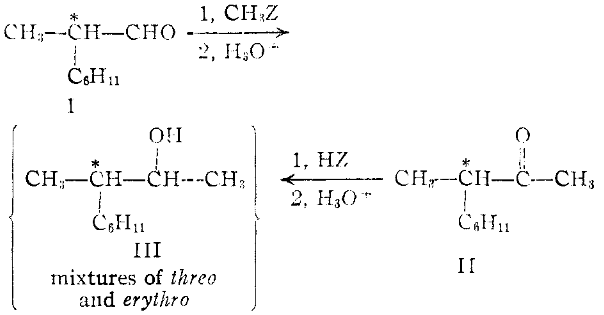
TABLE I

PHYSICAL PROPERTIES AND ANALYSES OF THE ISOMERS OF 3-CYCLOHEXYL-2-BUTANOL, THEIR DERIVATIVES AND PRECURSORS

Compound	Method prepn.[a]	Yield, %	$n^{25}D$	$\alpha^{25}D$ l 1 dm., neat	Mol. formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
D-*threo*-3-Cyclohexyl-2-butanol[b]	A	92	1.4698	−17.74°	$C_{10}H_{20}O$	76.86	76.81	12.90	12.79
L-*threo*-3-Cyclohexyl-2-butanol[b]	A	92	1.4698	+18.06	$C_{10}H_{20}O$	76.86	76.71	12.90	12.51
D-*erythro*-3-Cyclohexyl-2-butanol[b]	A	87	1.4700	− 2.58	$C_{10}H_{20}O$	76.86	77.02	12.90	12.61
L-*erythro*-3-Cyclohexyl-2-butanol[b]	A	87	1.4700	+ 2.54	$C_{10}H_{20}O$	76.86	76.90	12.90	13.03
D-*threo*-3-Cyclohexyl-2-acetoxybutane	B	90	1.4499	−11.80	$C_{12}H_{22}O_2$	72.68	72.55	11.18	11.18
L-*threo*-3-Cyclohexyl-2-acetoxybutane	B	90	1.4499	+12.06	$C_{12}H_{22}O_2$	72.68	72.63	11.18	11.03
D-*erythro*-3-Cyclohexyl-2-acetoxybutane	B	90	1.4497	+ 4.38	$C_{12}H_{22}O_2$	72.68	72.71	11.18	11.50
L-*erythro*-3-Cyclohexyl-2-acetoxybutane	B	90	1.4497	− 4.10	$C_{12}H_{22}O_2$	72.68	72.67	11.18	11.23
D-3-Cyclohexyl-2-butanone	C	84	....	+31.76	$C_{10}H_{18}O$	77.89	77.68	11.77	11.53
L-3-Cyclohexyl-2-butanone	C	86	1.4558	−31.14	.....	...	...	...	...
D-2-Cyclohexylpropanoic acid	..	81	....	.....	$C_9H_{16}O_2$	69.28	69.36	10.34	10.04
D-2-Cyclohexyl-1-propanol	..	91	1.4697	− 1.39	$C_9H_{18}O$	76.01	75.49	12.76	12.49

[a] See Experimental section for corresponding procedure. [b] The rotations of the isomeric 3-phenyl-2-butanols which served as starting materials are as follows (l 1 dm., neat): L-*threo*, $\alpha^{23}D$ +31.62°; D-*threo*, $\alpha^{23}D$ −31.06°; L-*erythro*, $\alpha^{23}D$ +0.94°; D-*erythro*, $\alpha^{23}D$ −0.88°.

Reference samples of the four optically pure stereoisomers of III of known configuration were readily preparable from the corresponding isomers of the thoroughly characterized 3-phenyl-2-butanol (IV) system.[6]



I

III
mixtures of *threo* and *erythro*

II

Results

Optically pure reference samples of the four stereomers of 3-cyclohexyl-2-butanol (III) were prepared by catalytic hydrogenation of the four corresponding optically pure samples of 3-phenyl-2-butanol (IV). Oxidation with *t*-butyl chromate of both D-*threo*-III and L-*threo*-III gave optically pure D-3-cyclohexyl-2-butanone (D-II) and L-3-cyclohexyl-2-butanone (L-II), respectively. Substantial evidence that little racemization occurred either during or after the oxidation is found in the equivalence of the rotations of three preparations of L-II ($\alpha^{25}D$ − 31.14°, $\alpha^{25}D$ − 30.80° and $\alpha^{25}D$ − 30.98°, l 1 dm., neat) in which the reaction times were varied from 24 to 72 hours. The equivalence of the magnitudes of the rotations of D-II and L-II ($\alpha^{25}D$ + 31.76° and $\alpha^{25}D$ − 31.14°, respectively, with l 1 dm., neat) further supports this contention. In an attempt to obtain optically pure 2-cyclohexylpropanol (I), optically pure 2-cyclohexylpropanol was oxidized by the same procedure used to convert alcohol III to ketone IV. Unfortunately considerable racemization and other side reactions accompanied the oxidation, and therefore the addition reactions were conducted with more readily available racemic I as starting material. Table I contains the physical properties and analyses of these compounds and derivatives. The additions to 2-cyclohexylpropanal (I) of methylmagnesium iodide in ether, of methyllithium in ether and of methyllithium in pentane were carried out utilizing racemic aldehyde. However, the reductions of 3-cyclohexyl-2-butanone (II) with lithium aluminum hydride in ether (both normal and inverse addition), sodium borohydride in methanol–water and aluminum isopropoxide in isopropyl alcohol were applied to optically pure ketone. To determine whether the product balance from the reduction of ketone II with aluminum isopropoxide was kinetically or thermodynamically controlled (the reaction is reversible), a deliberate attempt was made to equilibrate *threo*- and *erythro*-3-cyclohexyl-2-butanol utilizing the above reagent in combination with acetone.

The product balances in all of the above cases were determined utilizing the rather large differences between the infrared spectra of the two diastereomeric alcohols (III). Figure 1 plots optical density *vs.* percentage composition of synthetic mixtures of *threo*- and *erythro*-III at the four wave lengths most advantageous for analysis.[7] The compositions of the unknown mixtures were then determined from their optical densities, and a mean deviation of ±1% was obtained for the values at the various wave lengths. A completely independent scheme of analysis based on rotations of the alcohols III and their acetates was developed which served as a check on the spectral method. Figure 2 plots observed rotation *vs.* percentage composition of known mixtures of optically pure L-*threo*- and L-*erythro*-III as well as of their respective acetates. Since these plots

$$b\left[\frac{\alpha_{ba}}{\alpha_{aa}} - \frac{\alpha_{bc}}{\alpha_{ao}}\right] = \frac{1}{x}\left[\frac{\alpha_a}{\alpha_{aa}} - \frac{\alpha_c}{\alpha_{ac}}\right] \quad (1)$$

$$b\left[\frac{\alpha_{ba}}{\alpha_{aa}} - 1\right] = \left[\frac{(\alpha_a)}{\alpha_{aa}}\left(\frac{1}{x}\right) - 1\right] \quad (2)$$

where b = mole fraction *threo* alcohol (or acetate), $100(1 - x)$ = % racemization, α_a = observed rotation of unknown alcohol mixtures, α_c = observed rotation of unknown acetate mixture, α_{aa} = rotation of L(+)-*erythro*-III, α_{bo} = rotation of L(+)-*threo*-III, α_{ao} = rotation of L(−)-*erythro*-III acetate and α_{bo} = rotation of L(+)-*threo*-III acetate.

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(6) (a) D. J. Cram, THIS JOURNAL, **71**, 3863 (1949); (b) **74**, 2129 (1952).

(7) The absorption of racemic and optically pure isomers was demonstrated to be identical at these wave lengths.

TABLE II

ANALYSES OF MIXTURES OF *threo*- AND *erythro*-3-CYCLOHEXYL-2-BUTANOL (III)[a]

Run no.	Reactions with 2-cyclohexylpropanol[b]	Solvent	*erythro*-III in mixtures, % Infrared analyses[c] at λ =				Rotational analyses[d] of			General av.
			8.65 μ	9.70 μ	10.34 μ	11.40 μ	Alc.	Acet.	Av.	
1	CH_3MgI	Ether	..[e]	65.0	63.0	66.0	..	..	..	65
2	CH_3Li	Pentane	..[e]	59.0	61.0	60.0	..	..	..	60
3	CH_3Li	Ether	..[e]	57.0	55.0	54.0	..	..	..	55
	Reactions with 3-cyclohexyl-2-butanone[f]									
4	$LiAlH_4$ (normal addit.)	Ether	40.0	39.0	41.0	41.5	41.0	41.5	41.3	41
5	$LiAlH_4$ (inverse addit.)	Ether	43.5	41.0	40.5	43.0	42.0	42.5	42.3	42
6	$NaBH_4$ (normal addit.)	MeOH–H_2O	37.0	35.0	35.5	37.0	38.0	37.5	37.8	37
7	Al(*i*-prop)$_3$	$(CH_3)_2CHOH$	64.5	62.0	63.0	64.0	66.3	(8% racemic)[g]		65
	Equilibration of									
8	L(+)-*threo*-III[f]	$(CH_3)_2CHOH$[h]	28.0	25.0	23.0	23.0	20.5	(17% racemic)[g]		23
9	D(−)-*erythro* III[f]	$(CH_3)_2CHOH$[h]	52.0	54.0	43.0	48.0	51.0	(45% racemic)[g]		50

[a] For the polarimetric data used in constructing this table, see Experimental. [b] This material was racemic. [c] See Fig. 1 for plots of optical density *vs.* % composition of known mixtures. [d] See Fig. 2 for plots of observed rotations of known mixtures *vs.* % composition. [e] The values obtained at λ = 8.65 μ were not included, since they are obviously anomalous. Since runs 1, 2 and 3 had a common starting material which underwent self-condensation very readily, it is probable that these anomalous values are due to the presence of a small amount of impurity which absorbs very strongly at this wave length. The excellent agreement between the values obtained at the other three wave lengths attests to the general validity of the analyses. [f] Optically pure materials. [g] Calculated from equations 1 and 2. [h] Plus small amounts of acetone.

are linear, both the percentage racemization as well as the composition of an unknown mixture can be calculated through the solutions of equations 1 and 2,[8] if the rotations of the alcohol and derived acetate mixtures are known. In those reactions in which the starting material was optically pure but some racemization occurred (*i.e.*, those involving aluminum isopropoxide), the above equation was applied. In the other reductions of 3-cyclohexyl-2-butanone no racemization occurred, and the percentage compositions of the products were determined from their rotations and the plots of Fig. 2. Table II records the results of these analyses as applied to the products of the various reactions. The agreement between the two methods of analysis appears to be within about 1%.

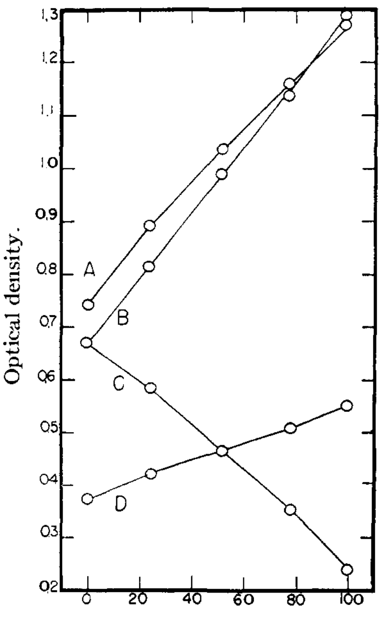

Fig. 1.—Plots of optical density *vs.* % composition of mixtures of *threo*- and *erythro*-3-cyclohexyl-2-butanol (III) at four wave lengths in the infrared: curve A, λ 9.70 μ; curve B, λ 8.65 μ; curve C, λ 10.34 μ; curve D, λ 11.40μ. Data obtained with Beckman IR2, NaCl prism, homogeneous films, 0.03 mm. thick.

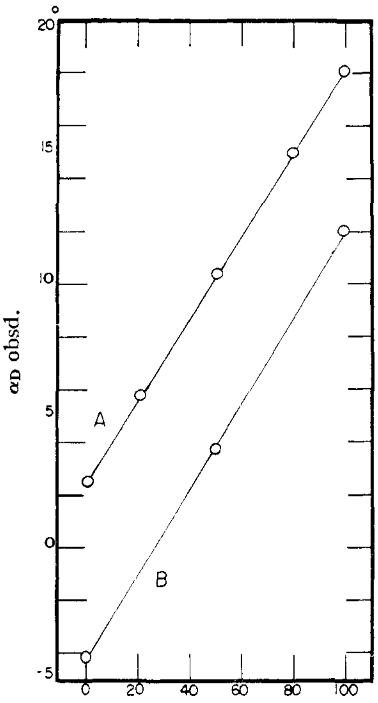

Fig. 2.—Curve A, plot of observed rotation (*l* 1 dm., neat) *vs.* % composition of mixtures of L-*erythro* and L-*threo*-3-cyclohexyl-2-butanol; curve B, plot of observed rotation *vs.* % composition of mixtures of L-*erythro* and L-*threo*-3-cyclohexyl-2-butyl acetate.

Discussion

Prior to the present investigation, the starting carbonyl compounds whose reactions illustrated

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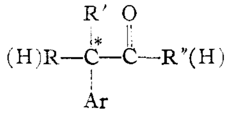
[8] In deriving these equations the reasonable assumption is made that each isomeric alcohol is racemized to the same extent. Any racemization that occurs must involve material containing only one asymmetric carbon atom, *e.g.*, the aldehyde or ketone.

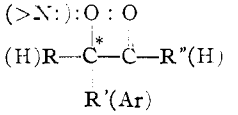
the rule of Steric Control of Asymmetric Induction all belonged to one of the two structural types illustrated by V and VI. Satisfactory explana-



$$(H)R-\overset{R'}{\underset{Ar}{\overset{*}{C}}}-\overset{O}{\overset{\|}{C}}-R''(H)$$

Ar = large group

V

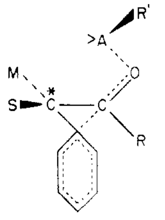


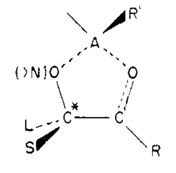
$$(H)R-\overset{(>N:):O}{\underset{R'(Ar)}{\overset{*}{C}}}-\overset{:O}{C}-R''(H)$$

:O:(>N:) = medium group

VI

tions for the existence of the above correlation can be applied to these two reaction types by invoking participation (in a polar sense) in the reaction's transition state of one of the groups attached to the asymmetric carbon of the starting material. Thus with VI as a starting material, a complex such as VI′ can be envisioned as a precursor to the transition state, whereas in the case of V, a complex such as V′ might be equally effective in freezing out other rotational conformations. Strong indication for π-orbital overlap of the sort shown in V′ is found



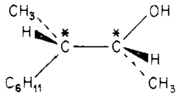


V′ A = Mg, Li, Na etc. VI′

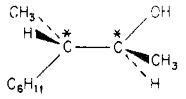
in the fact that the ultraviolet absorption spectra of α-arylketones are different from that expected if the carbonyl and aryl groups are isolated chromophores.[9] Furthermore, the ability of reagents such as the Grignard, lithium aluminum hydride, etc., to coördinate with unshared pairs of electrons of oxygen and nitrogen is well known,[10] and a five-membered ring such as VI′ might be quite stable.

On the other hand, a general explanation for the operation of the rule which depends entirely on steric factors is as follows. The reagents involved in the reactions in question all involve metals with coördination numbers of four or more, and they probably coördinate with the carbonyl group of the starting material as well as with solvent.[10] The carbonyl oxygen therefore might well become effectively the bulkiest group in the molecule and tend to orient itself between the two least bulky groups attached to the adjacent asymmetric carbon atom. The asymmetric carbons of 2-cyclohexylpropanal (I) or 3-cyclohexyl-2-butanone (II) do not carry any groups capable of becoming involved in a polar sense in the reactions in question. Thus the applicability of the rule to the reactions of I and II is a criterion of whether a purely steric explanation applies. The data of Chart I indicate that in runs 1–6 the rule predicts the isomer that predominates in the product. Thus the above purely steric explanation for the existence of the correlation represented by the rule is preferable to the other two explanations, "at least for the general case."

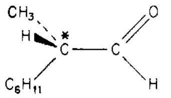
CHART I



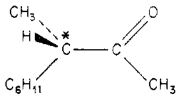
D-*threo*-III



D-*erythro*-III



D-I[a]



D-II[b]

$C_6H_{11} > CH_3 > H$ in effective bulk

	Run	Reagents		
	1	CH_3MgI in ether	1	1.9
	2	CH_3Li in pentane	1	1.5
	3	CH_3Li in ether	1	1.2
	4	$LiAlH_4$ (normal add.)	1.4	1
	5	$LiAlH_4$ (inverse add.)	1.4	1
	6	$NaBH_4$ in $MeOH-H_2O$	1.7	1
	7	Al (*i*-prop.)$_3$	1	1.9
D-*threo*-III[c]	8	Al (*i*-prop.)$_3$·acetone	3.3	1
D-*erythro*-III	9	Al (*i*-prop.)$_3$·acetone	1	1

[a] Actually, racemic material was utilized. [b] Actually, L-II was used. [c] L-*threo*-III was actually used. Since the results would have been the same had D-*threo*-III been used, space is saved by formulating the results as above.

Comparison of the product distribution data obtained in the 3-cyclohexyl-2-butanol and 3-phenyl-2-butanol syntheses reveals a number of interesting relationships. Thus in the reaction of methylmagnesium bromide with 2-phenylpropanal, the predominance of *erythro* over *threo* product was 2/1,[2a] whereas with cyclohexyl in place of phenyl (run 1) the ratio was 1.9/1. In the reduction of 3-phenyl-2-butanone with lithium aluminum hydride the predominance of *threo* over *erythro* product was 2.5/1,[2a] whereas with cyclohexyl in place of phenyl (run 4) the ratio amounted to 1.4. Thus the phenyl induced about the same steric selectivity as the cyclohexyl group in the reactions involving Grignard reagent, and a somewhat greater selectivity in the reactions involving lithium aluminum hydride.[11]

As might be expected on the basis of the above explanation, more stereochemical selectivity is found in run 1 than in run 3. Runs 2 and 3 cannot be compared in a similar way because the former was a heterogeneous and the latter a homogeneous reaction. A higher selectivity of a Grignard reagent over an alkyl lithium was previously noted in the syntheses of the diastereomers of the 3,4-dimethyl-4-phenyl-3-hexanol system.[2b] Within experimental error no difference was noted between the results obtained in run 4 in which ketone II was added to a large excess of lithium aluminum hydride and run 5 in which inverse addition was employed. This result suggests that the second, third and fourth hydrogens of lithium aluminum

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[9] W. D. Kumler, L. A. Strait and E. L. Alpen, THIS JOURNAL, **72**, 1463 (1950); E. L. Alpen, W. D. Kumler and L. A. Strait, *ibid.*, **72**, 4558 (1950); S. Winstein, M. Brown, K. C. Schreiber and A. H. Schlesinger, *ibid.*, **74**, 1144 (1952); D. J. Cram and J. D. Knight, *ibid.*, **74**, 5835 (1952); W. B. Bennet and A. Burger, *ibid.*, **75**, 84 (1953).

[10] An interesting demonstration of this ability was reported by H. L. Cohen and G. F. Wright, Abstracts Papers Presented at Buffalo Meeting, American Chemical Society, p. 32K (1952).

[11] In paper XXI of this series [D. J. Cram, F. A. Abd Elhafez and H. LeRoy Nyquist, THIS JOURNAL, **76**, in press (1954)] quite different data suggest that a phenyl is effectively bulkier than an isopropyl group.

hydride react faster than the first. Had different hydrogens of lithium aluminum hydride been involved in runs 4 and 5, the steric situations would have been different, and the balance of products would probably have been affected. Sodium borohydride in methanol–water appears to be more selective (run 6) than lithium aluminum hydride in ether (runs 4 and 5), a fact that may be attributable more to the solvent than to the reducing agent.

The results of the reaction of aluminum isopropoxide with ketone II (run 7) are clearly inconsistent with the rule. To determine whether the products were kinetically or thermodynamically controlled, a deliberate attempt was made to equilibrate each isomer of III (runs 8 and 9). Although equilibrium was not reached in seven days, the reactions had gone far enough to indicate that an equilibrium mixture would contain between about 23% and 50% of the *erythro* isomer.[12] Since in run 7 the reaction time was only about an hour, and since *erythro*-III predominated in the product by a factor of 1.9 to 1, it appears that the product ratio was largely kinetically controlled. This result clearly indicates that the rule is not applicable to predicting the steric course of aluminum isopropoxide reductions of ketones, and that other steric factors operate in this reaction that are either absent or not important in the other reductions (*e.g.*, LiAlH$_4$, NaBH$_4$, etc.). Another interesting difference between run 7 on the one hand and runs 4, 5, and 6 on the other is that a small amount of racemization accompanied reduction in the former case, whereas none did in the latter cases. It is noteworthy that racemization followed closely behind equilibration in runs 8 and 9, a fact that suggests that the two reactions have a common intermediate.

Experimental

Reductions of Stereoisomers of 3-Phenyl-2-butanol (IV) to Stereoisomers of 3-Cyclohexyl-2-butanol (III). Procedure A.—The four optically pure starting materials (IV) were prepared as described previously[6] (see Table I). The preparation of D(−)-*erythro*-3-cyclohexyl-2-butanol is illustrative.

A solution of 5 g. of D(−)-*erythro*-3-phenyl-2-butanol in 50 ml. of glacial acetic acid was shaken mechanically at a hydrogen pressure of 40 lb./sq. inch with 1 g. of platinum oxide until no more hydrogen was absorbed. The mixture was filtered into water and the resulting mixture was extracted with pure pentane.[13] The pentane layer was washed with water, with 3 *N* sodium carbonate solution, water, and then dried over magnesium sulfate. Removal of the solvent and two flash distillations of the residue gave 4.8 g. of material. The infrared absorption spectrum showed the presence of an acetate band at 5.8 μ. The sample was treated with lithium aluminum hydride in ether and worked up in the usual way, giving 4.5 g. of pure D(−)-*erythro*-3-cyclohexyl-2-butanol. In the case of the *threo*-alcohols pure material was obtained directly from the hydrogenation reaction, obviating the lithium aluminum hydride step.

Preparation of the Stereoisomeric 3-Cyclohexyl-2-acetoxybutanes. Procedure B.—A solution of 1 g. of the alcohol, 10 ml. of pyridine and 6.5 ml. of acetic anhydride was heated at 100° for 12 hours. Decomposition of the resulting mixture in dilute, ice-cold sulfuric acid was followed by extraction of the acetate with pentane. The pentane layer was washed with water, 3 *N* sodium carbonate solution, water, and then dried. Evaporation of the solvent through a short column and two flask distillations of the residual oil afforded the acetate in a pure state.

Preparation of the Stereoisomeric 3-Cyclohexyl-2-butanones. Procedure C.—The preparation of L(−)-3-cyclohexyl-2-butanone is illustrative. A dry solution of *t*-butyl chromate in pentane (prepared from 9.0 g. of *t*-butyl alcohol and 4 g. of chromic anhydride in 50 ml. of pentane) was added dropwise and with stirring to an ice-cold solution of 4 g. of L(+)-*threo*-3-cyclohexyl-2-butanol in 20 ml. of pentane. After the addition was complete, the solution was stirred at room temperature for 48 hours. The dark mixture was cooled, and the excess oxidant was decomposed by the slow addition of a solution of 6 g. of oxalic acid in 60 ml. of water. The mixture was stirred for an additional 45 minutes. The pentane layer was separated, and the aqueous phase was extracted twice with pentane. The combined fractions were washed with water, 3 *N* sodium carbonate solution, water, and then dried. The pale yellow solution was passed through a 20-g. column of neutral alumina in pentane, with 300 ml. of additional pentane as eluant. Removal of the pentane through a short Vigreux column and two flash distillations of the residual oil yielded 3.3 g. of colorless product. The dinitrophenylhydrazone (orange plates from ethanol–water) melted at 62–66° after three recrystallizations. The range is probably due to partial racemization.

Anal. Calcd. for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63. Found: C, 57.44; H, 6.38.

Preparation of D(+)-2-Cyclohexylpropionic Acid.—A sample of 16.7 g. of D(+)-2-phenylpropionic acid[14] ($[\alpha]^{25}\text{D}$ +99.34°, neat) was hydrogenated at room temperature in 30 ml. of glacial acetic acid at a pressure of 40 lb./sq. inch with 1 g. of platinum oxide. Filtration of the mixture into water, extraction of the acid with pentane, and the customary work-up of the pentane layer afforded 15.5 g. of product. Two recrystallizations from pentane at −80° gave 14.0 g. of D(+)-2-cyclohexylpropionic acid, m.p. 46.0–46.5°, $[\alpha]^{25}\text{D}$ +18.9° (*c* 10%, ethanol).

Preparation of 2-Cyclohexyl-1-propanol.—A 5-g. sample of D(+)-2-cyclohexylpropionic acid was reduced with 1.5 g. of lithium aluminum hydride in ether in the usual way to give after two flash distillations 4.15 g. of D(−)-2-cyclohexyl-1-propanol.

Because of the low yields encountered in the preparation of pure 2-cyclohexylpropanal from the alcohol, it was necessary to prepare a large amount of racemic 2-cyclohexyl-1-propanol. Hydratropic aldehyde[5a] (freshly distilled, b.p. 204–204.5° (1 atm.)), 35 g. in 75 ml. of ether, was reduced with lithium aluminum hydride to give 32.8 g. of 2-phenyl-1-propanol. This material was dissolved in 100 ml. of glacial acetic acid and hydrogenated catalytically with platinum oxide. The crude product was isolated and treated with 15 g. of potassium hydroxide in 50% aqueous methanol to hydrolyze the small amount of acetate present. Extraction of the mixture with pentane followed by two flash distillations of the product (the first 3 ml. was discarded) gave 27.5 g. of 2-cyclohexyl-1-propanol, $n^{25}\text{D}$ 1.4697.

Oxidation of 2-Cyclohexyl-1-propanol to 2-Cyclohexylpropanal (I).—To a cooled solution of 2 g. of the alcohol (D-(−)) in 10 ml. of pentane was added dropwise and with stirring a dry solution of *t*-butyl chromate (prepared from 4.5 g. of *t*-butyl alcohol, 2 g. of chromic anhydride and 25 ml. of pentane). After 48 hours at room teperature, the mixture was decomposed by the slow addition of a solution of 3 g. of oxalic acid in 30 ml. of water. Extraction of the mixture with pentane, washing of the pentane layer with water, with 3 *N* sodium carbonate solution, and with water, and drying, gave a pale yellow solution. This solution was chromatographed on 10 g. of neutral alumina, with 200 ml. of pentane as eluant. Evaporation of the solvent through a short column and two flash distillations of the residual oil gave 0.5 g. of impure aldehyde, $n^{25}\text{D}$ 1.4538, $[\alpha]^{25}\text{D}$ +8.22° (*l* 1 dm., neat). The degree of racemization of this material is not known, and the refractive index is 0.0012 low, as seen from the following.

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[12] Since these reactions were carried out under almost equivalent conditions, and since the rates at which each isomer goes to the equilibrium mixture should be equal, the data suggest that at equilibrium the mixture would contain predominantly *threo* material. An analysis of the steric situation in each isomer similar to the analysis applied to the diastereomers of 1,2-diphenyl-2-propyl formate [see F. A. Abd Elhafez and D. J. Cram, THIS JOURNAL, **75**, 339 (1953)] indicates that on theoretical grounds, *threo*-III should be the more thermodynamically stable isomer.

[13] All the pentane used had been fractionally distilled through a forty plate column.

[14] F. A. Abd Elhafez and D. J. Cram, THIS JOURNAL, **74**, 5847 (1952).

The oxidation of 12.6 g. of racemic alcohol by the above procedure gave 3.5 g. of crude product. This material was shaken with 15 ml. of a 40% aqueous solution of sodium bisulfite for 20 minutes. The milky mixture was diluted with water and extracted with two 10-ml. portions of pentane. The aqueous phase was made alkaline by the addition of 100 ml. of 3 *N* sodium carbonate solution, and then extracted with pentane. After the pentane layer was washed and dried, the solvent was evaporated through a short column and two flash distillations of the residual oil gave 1.1 g. of the desired aldehyde, b.p. 80° (bath temperature) (16 mm.), $n^{25}\text{D}$ 1.4550. The dinitrophenylhydrazone melted at 140–141°.

Anal. Calcd. for $C_{15}H_{20}O_4N_4$: C, 56.23; H, 6.29. Found: C, 56.40; H, 6.11.

Reductions of L(−)-3-Cyclohexyl-2-butanone. (a) Lithium Aluminum Hydride.—A solution of lithium aluminum hydride in ether was prepared by mechanical shaking of 7.5 g. of the reagent with 60 ml. of anhydrous ether for one hour, followed by filtration of the resulting mixture. The slightly opaque solution was divided into equal parts.

(1) **Normal Addition.**—A solution of 3 g. of L(−)-3-cyclohexyl-2-butanone in 20 ml. of dry ether was added dropwise and with stirring to 30 ml. of the ethereal lithium aluminum hydride solution. The solution was stirred overnight at room temperature. After decomposition of the excess reagent with water, the mixture was poured into ice-cold 3 *N* sodium hydroxide solution and extracted three times with pentane. The pentane solution was washed with water and dried. Removal of the pentane (short column) and two flash distillations of the residual oil gave 2.05 g. of colorless oil, $n^{25}\text{D}$ 1.4699, $[\alpha]^{25}\text{D}$ +11.62° (*l* 1 dm., neat). One gram of this material was acetylated to give 0.9 g. of oil, $n^{25}\text{D}$ 1.4498, $[\alpha]^{25}\text{D}$ +5.10° (*l* 1 dm., neat).

(2) **Inverse Addition.**—A 30-ml. portion of the lithium aluminum hydride solution was added very slowly and with stirring to a solution of 3 g. of L(−)-ketone in 20 ml. of ether. After stirring overnight the reaction 'mixture' was worked up as above, giving 2.3 g. of a mixture of *threo-* and *erythro*-alcohols, $n^{25}\text{D}$ 1.4699, $[\alpha]^{25}\text{D}$ +11.50° (*l* 1 dm., neat). The physical constants of the derived acetate mixture were $n^{25}\text{D}$ 1.4498, $[\alpha]^{25}\text{D}$ +4.94° (*l* 1 dm., neat).

(b) **Sodium Borohydride.**—To a solution of 1 g. of the ketone in 25% aqueous methanol was added 0.5 g. of sodium borohydride. The mixture was left at room temperature for one hour, and then heated for an additional hour. The product was isolated in the usual fashion, giving 0.9 g. of material, $n^{25}\text{D}$ 1.4698, $[\alpha]^{25}\text{D}$ +12.18° (*l* 1 dm., neat). Conversion to the acetate mixture gave material with $n^{25}\text{D}$ 1.4496, $[\alpha]^{25}\text{D}$ +5.76° (*l* 1 dm., neat).

(c) **Aluminum Isopropoxide.**—A solution of 0.75 g. of the L-(−) ketone, 6 g. of aluminum isopropoxide (Eastman Kodak Co. product, purified by distillation), and 30 ml. of isopropyl alcohol (purified by distillation from calcium oxide) was heated to reflux, allowing the vapor to pass through a Widmer column, then through a water-jacketed condenser. The heat input was adjusted to maintain a vapor temperature between 70–80°. After an hour the distillate gave a negative test for acetone. The bulk of the isopropyl alcohol was removed under reduced pressure, and the residue was hydrolyzed with ice-cold dilute hydrochloric acid. Pentane extraction of the product followed by the usual work-up gave 0.7 g. of alcohol mixture, $n^{25}\text{D}$ 1.4698, $[\alpha]^{25}\text{D}$ +7.20° (*l* 1 dm., neat). The derived acetate mixture had $n^{25}\text{D}$ 1.4496, $[\alpha]^{25}\text{D}$ +1.06° (*l* 1 dm., neat).

Attempted Equilibration of L(+)-*threo*- and of D(−)-*erythro*-3-Cyclohexyl-2-butanol.—A solution of 1.6 g. of L-(+)-*threo*-3-cyclohexyl-2-butanol and 1.5 g. of aluminum isopropoxide in 3 ml. of acetone and 3 ml. of isopropyl alcohol was heated under reflux for seven days. The acetone was removed through a Widmer column, and the residue was worked up as before. The product after two flash distillations amounted to 1 g. of pale yellow oil, $n^{25}\text{D}$ 1.4642. Acetylation and purification of the acetate by chromatographic procedure, first on neutral alumina, then on basic alumina, gave material with $n^{25}\text{D}$ 1.4512, $[\alpha]^{25}\text{D}$ +5.26° (*l* 1 dm., neat). Reconversion to the alcohol mixture by use of lithium aluminum hydride and purification of the alcohol by passage through basic alumina yielded 0.4 g. of product, $n^{25}\text{D}$ 1.4690, $[\alpha]^{25}\text{D}$ +12.34° (*l* 1 dm., neat). The acetylated product had $n^{25}\text{D}$ 1.4508 and $[\alpha]^{25}\text{D}$ +7.26° (*l* 1 dm., neat).

One gram of D(−)-*erythro*-3-cyclohexyl-2-butanol was subjected to the above conditions. Isolation and purification procedures identical to those described above were necessary to effect purification of the desired butanol mixture. The physical constants of the alcohol mixture thus obtained were, $n^{25}\text{D}$ 1.4701, $[\alpha]^{25}\text{D}$ −5.54° (*l* 1 dm., neat), the derived acetate mixture, $n^{25}\text{D}$ 1.4512, $[\alpha]^{25}\text{D}$ −2.04° (*l* 1 dm., neat). Although the above yields are low, the losses of product are non-selective in a stereochemical sense, and therefore the products are probably representative.

Reactions of Racemic 2-Cyclohexylpropanal. (a) Methylmagnesium Iodide.—To a twenty-fold excess of methylmagnesium iodide in 100 ml. of ether was added 1.0 g. of racemic aldehyde in 10 ml. of ether. The solution was stirred overnight at room temperature. Decomposition of the resulting mixture with water, and pentane work-up in the usual fashion gave 1.0 g. of a mixture of *threo-* and *erythro*-3-cyclohexyl-2-butanol, $n^{25}\text{D}$ 1.4699. The derived acetate mixture has $n^{25}\text{D}$ 1.4496.

(b) **Methyllithium.**—A solution of methyllithium in ether was prepared from 30 g. of methyl iodide, 3.18 g. of lithium ribbon and 200 ml. of ether. This solution was 1.0 *N* in methyllithium, 5 ml. of the solution requiring 9.5 ml. of 0.53 *N* hydrochloric acid for neutralization to methyl red end-point.

(1) **Reaction in Ether.**—To 75 ml. of the filtered 1 *N* methyllithium solution (a fifteen-fold excess) was added 0.5 g. of 2-cyclohexylpropanal in 10 ml. of ether. Pentane work-up afforded 0.54 g. of product, $n^{25}\text{D}$ 1.4697. The derived acetate mixture had $n^{25}\text{D}$ 1.4496.

(2) **Reaction in Pentane.**—Under nitrogen, 75 ml. of the 1 *N* methyllithium solution was evaporated to dryness. Two hundred ml. of pentane was added (methyllithium is quite insoluble in this solvent). With stirring, 0.5 g. of the aldehyde in 10 ml. of pentane was added to the mixture. The mixture was stirred overnight and worked up in the usual fashion, giving 0.52 g. of material, $n^{25}\text{D}$ 1.4697. The derived acetate mixture has $n^{25}\text{D}$ 1.4496.

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