The Stereochemistry of Nucleophilic Addition. I. The Reformatsky Reaction of 2-Methyl- and 2-Ethylcyclohexanones[1)]

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(Received September 24, 1970)

The Reformatsky reaction of 2-methyl- or 2-ethylcyclohexanone with ethyl bromoacetate gave a mixture of epimeric alcohols, which were then separated by column chromatography in an 80 : 20 ratio. The configurations of these major and minor products were identified as ethyl *trans*- and ethyl *cis*-2-methyl (or ethyl)-1-hydroxycyclohexylacetate respectively on the basis of their IR analyses, their chromatographic behavior, and correlation with the products of the Grignard reaction, the stereochemistry of which is well known. The NMR spectra of these epimeric alcohols are also discussed, and it is suggested that the chemical shifts of the methylene protons alpha to the ethoxycarbonyl group and of the proton of the hydroxyl group gives useful data for their stereochemical assignments. From these results, it is evident that the Reformatsky and the Grignard reactions proceed in a similar fashion; that is, the entering group predominantly approaches to the carbonyl group from the equatorial side. The stereoselectivity of the Reformatsky reaction is slightly less than that of the Grignard reaction.

The Reformatsky reaction[2)] has been utilized for over eighty years as a convenient method for preparing β-hydroxy-carboxylic esters, which in turn can be converted to the corresponding unsaturated esters and acids. However, the stereochemistry of this reaction with cyclic ketones containing a substituent in the position alpha to the carbonyl group has been little studied.

Recently Epstein and Sonntag[3)] reported that the condensation of 2-chlorocyclohexanone with methyl bromoacetate gives only one diastereomer, methyl *trans*-2-chloro-1-hydroxycyclohexylacetate. More recently, the Reformatsky reactions of monocyclic terpenes ((—)-menthone, (+)-isomenthone, and (—)-carvomenthone) with ethyl bromoacetate have also been reported by Perry and Maroni-Barnaud;[4)] the stereochemistry of the major products in these reactions assigned the *trans*-configuration of the ester group to the alpha-substituted alkyl group.

During the course of other synthetic experiments in this laboratory, we also studied the stereochemistry of the Reformatsky reaction with 2-methyl- and 2-ethylcyclohexanones; the present paper will describe our results.

The condensation of 2-methylcyclohexanone (I) with ethyl bromoacetate is known to yield ethyl 2-methyl-1-hydroxycyclohexylacetate (II),[5)] but the composition of the mixture of the isomers formed was not examined. In the present study, this reaction was reinvestigated in more detail; the results are summarized in Table 1, which lists the average values obtained from two or more determinations. It can be seen from Table 1 that a good yield (84%) of the β-hydroxy ester was obtained by the use of an excess of the bromoester and zinc in a benzene solution, while when tetrahydrofuran was used as the solvent in place of benzene, the yield was somewhat low (63%). The distilled product was successfully separated by means of column chromatography on sillica gel to give two epimeric oily esters (IIa and IIb) in an approximately 80: 20 ratio. Each of these esters (IIa and IIb) was converted to the corresponding crystalline acid (IIIa, mp 78—79°C and IIIb, mp 80—81°C) by alkaline hydrolysis. The reported melting point for 2-methyl-1-hydroxycyclohexylacetic acid is 67—68°C;[5)] this substance is apparently a mixture of the epimers (IIIa and IIIb), thus accounting for the lower melting point. The acids (IIIa and IIIb) were further characterized as their *p*-bromophenacyl esters (IVa, mp 86—88°C and IVb, mp 91.5—92.5°C, respectively). The configurations of IIa and IIb are assigned on the basis of the following evidence. The reduction of IIa and IIb with $LiAlH_4$ in ether afforded, respectively, the corresponding diols (Va, mp 67—68°C and Vb, liquid). Subsequently, Va and Vb were subjected to tosylation with *p*-toluenesulfonyl chloride in pyridine, followed by the reduction of the resulting tosylates (VIa and VIb) with $LiAlH_4$ in tetrahydrofuran; this gave the epimeric 2-methyl-1-ethylcyclohexanols, VIIa and VIIb, respectively.

Since it is well known[6—8)] that the Grignard reaction of 2-alkylcyclohexanones with simple alkylmagnesium halides yields *cis*-2-alkylcyclohexanol derivatives possessing an axial hydroxyl group as the major product, the preparation of the epimeric 2-methyl-1-ethylcyclohexanols by the Grignard reaction was attempted in order to make possible direct comparisons with the above alcohols (VIIa and VIIb). Although the Grignard reaction of I with ethylmagnesium iodide has already been reported by Cook and Laurence[9)] the composition of the epimeric alcohols was not examined. Therefore, the separation of the epimers was carried out by means

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1) Although the formulas depicted represent only one enantiomer, they are taken to indicate a racemate.

2) S. Reformatstky, *Ber.*, **20**, 1210 (1887). For a review of this, see R. L. Shriner, "Organic Reactions", Vol. 1, Wiley, New York (1942), p. 1.

3) W. W. Epstein and A. C. Sonntag, *Tetrahedron Lett.*, **1966**, 791.

4) M. Perry and Y. Maroni-Barnaud, *Bull. Soc. Chim. Fr.*, **1969**, 3574.

5) O. Wallach and E. Beschke, *Ann. Chem.*, **347**, 337 (1906); K. Auwers and Ph. Ellinger, *ibid.*, **387**, 230 (1912).

6) A. V. Kamernitzky and A. A. Akhren, *Tetrahedron*, **18**, 705 (1962), and the references cited therein.

7) H. O. House and W. L. Respess, *J. Org. Chem.*, **30**, 301 (1965).

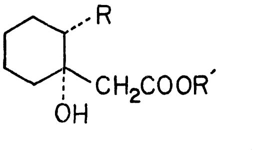
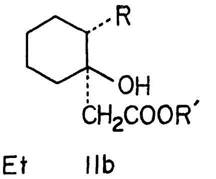
8) F. Rocquet, J. P. Battioni, M. L. Capman, and W. Chodkiewicz, *C. R. Acad. Sci.*, **268**, 1449 (1969); *Chem. Abstr.*, **71**, 29919h (1969).

9) J. W. Cook and C. A. Laurence, *J. Chem. Soc.*, **1938**, 58.

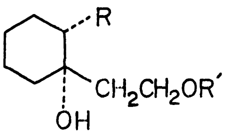
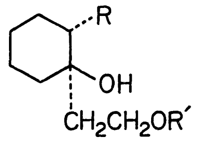
Table 1. The data of the Reformatsky reaction

	Starting substance (mol)			Solvent[a)]	Product		Ratio of epimers[b)]	
	Ketone	$BrCH_2CO_2Et$	Zn		Bp (°C/mmHg)	Yield[b)] (%)	*trans*	*cis*
I	0.050	0.050	0.050	B	119—122/10	68	80	20
	0.050	0.075	0.075	B	119—122/10	84	81	19
	0.050	0.075	0.075	THF	127—129/15	63	75	25
VIII	0.040	0.060	0.060	B	137—141/14	83	80	20

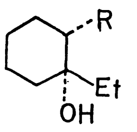
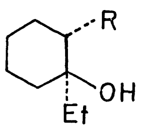
a) Solvent abbreviations: B=Benzene, THF=tetrahydrofuran.
b) The individual values obtained differ from these average values by not more than ±1%.

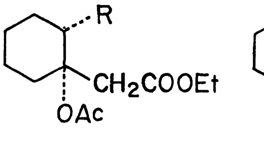
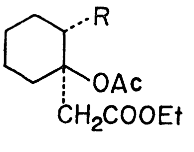
IIa	R=Me, R'=Et	IIb
IIIa	R=Me, R'=H	IIIb
IVa	R=Me R'=p-Br-phenacyl	IVb
IXa	R=R'=Et	IXb

Va	R=Me, R'=H	Vb
VIa	R=Me, R'=Ts	VIb
Xa	R=Et, R'=H	Xb
XIa	R=Et, R'=Ts	XIb

VIIa	R=Me	VIIb
XIIa	R=Et	XIIb

XIIIa	R=Me	XIIIb
XIVa	R=Et	XIVb

of column chromatography; two epimeric alcohols were thus successfully separated in a 90: 10 ratio. The major and minor alcohols of this reaction were shown to be identical with VIIa and VIIb respectively by comparisons of their IR and NMR spectra.

Similarly, 2-ethylcyclohexanone (VIII) was also condensed with ethyl bromoacetate to give an 83% yield of epimeric β-hydroxy-carboxylic esters, which were then separated into IXa (liquid) and IXb (mp 50.5—51.5°C) in an 80:20 ratio. The reduction of the major (IXa) and minor (IXb) esters with $LiAlH_4$ gave the corresponding diols (Xa, mp 93.5—94.5°C and Xb, mp 73—73.5°C), which were then further converted to the corresponding 1,2-diethylcyclohexanols (XIIa and XIIb) *via* tosylates (XIa and XIb). The Grignard reaction[10)] of VIII with ethylmagnesium bromide gave epimeric alcohols in a 93:7 ratio; these major and minor alcohols were also shown to be identical with XIIa and XIIb respectively.

The IR spectra of IIa, IIb, IXa, and IXb are summarized in Table 2, in which the hydroxyl absorption bands have been assigned by comparing their spectra with those of the corresponding acetates (XIIIa, XIIIb, XIVa, and XIVb). The IR spectra of IIa and IXa showed bands at 988 cm^{-1} and at 986 cm^{-1} respectively; they suggest the presence of the axial hydroxyl groups, while in the cases of IIb and IXb their spectra (IIb: 1050 cm^{-1} and IXb: 1056 cm^{-1}) suggest the presence of the equatorial hydroxyl groups. These stereochemical assignments of the hydroxyl groups were further supported by the chromatographic behavior of mixtures of isomeric alcohols. Winstein and Holness[11)] have stated that isomers with equatorial hydroxyl groups can be expected to be adsorbed more strongly on chromatography and, therefore, to be more difficult to elute than the isomers with the more hindered axial hydroxyls. In the present study, the isomers (IIa, VIIa, IXa and XIIa) assigned to the axial hydroxyl group were eluted first in each instance.

Table 2. The IR spectra of IIa, IIb, IXa and IXb in $CHCl_3$ (cm^{-1})

	IIa	IXa	IIb	IXb
OH	3512	3512	3512	3520
	988	986	1050	1056
C=O	1710	1710	1708	1708

The NMR spectra are shown in Tables 3–7. It is of interest to note the difference in the signals due to methylene protons alpha to the ethoxycarbonyl group. As is shown in Tables 3 and 4, the methylene protons of

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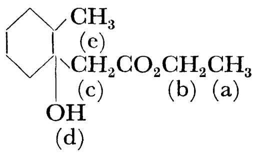
[10)] J. R. Dice, L. E. Loveless, Jr., and H. L. Cates, Jr., *J. Amer. Chem. Soc.*, **71**, 3546 (1949).

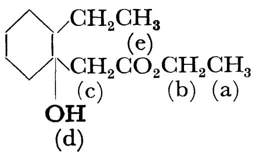
[11)] S. Winstein and N. Holness, *ibid.*, **77**, 5562 (1955).

TABLE 3. THE NMR SPECTRA OF ETHYL 1-HYDROXY-2-METHYLCYCLOHEXYLACETATES



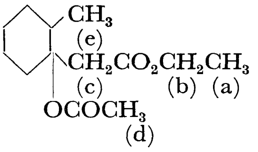
		a	b	c	d	e
IIa (major)	$CDCl_3$	1.27 (t, J=7.0)	4.15 (q, J=7.0)	2.29 (d, J=15) 2.68 (d, J=15)	3.07 (bs)	0.92
	Py-d_5	1.14 (t, J=7.0)	4.12 (q, J=7.0)	2.71 (s)	—	1.10 (d, J=5.0)
	Δ[12]	+0.13	+0.03	−0.22	—	−0.18
IIb (minor)	$CDCl_3$	1.28 (t, J=7.0)	4.17 (q, J=7.0)	2.48 (s)	3.64 (bs)	0.92 (d, J=6.0)
	Py-d_5	1.13 (t, J=7.0)	4.13 (q, J=7.0)	2.58 (s)	—	1.03 (d, J=6.5)
	Δ[12]	+0.15	+0.04	−0.10	—	−0.11

TABLE 4. THE NMR SPECTRA OF ETHYL 1-HYDROXY-2-ETHYLCYCLOHEXYLACETATES



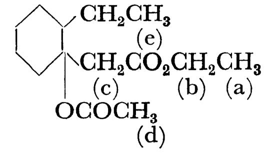
		a	b	c	d	e
IXa (major)	$CDCl_3$	1.28 (t, J=7.0)	4.18 (q, J=7.0)	2.33 (d, J=15) 2.76 (d, J=15)	*ca* 2.9 (bs)	0.87 (t, J=6.0)
	Py-d_5	1.16 (t, J=7.0)	4.15 (q, J=7.0)	2.78 (s)	—	0.90 (t, J=7.0)
	Δ[12]	+0.12	+0.03	−0.24	—	−0.03
IXb (minor)	$CDCl_3$	1.29 (t, J=7.0)	4.20 (q, J=7.0)	2.47 (d, J=16) 2.56 (d, J=16)	3.65 (bs)	0.95 (t, J=4.0)
	Py-d_5	1.14 (t, J=7.0)	4.14 (q, J=7.0)	2.61 (s)	—	0.94 (t, J=4.5)
	Δ[12]	+0.15	+0.06	−0.10	—	+0.01

TABLE 5. THE NMR SPECTRA OF THE ACETATE (XIIIa AND XIIIb) IN $CDCl_3$



	a	b	c	d	e
XIIIa	1.23 (t, J=7.0)	4.07 (q, J=7.0)	2.79 (d, J=14) 3.27 (d, J=14)	1.99 (s)	0.96 (d, J=7.0)
XIIIb	1.23 (t, J=7.0)	4.09 (q, J=7.0)	2.75 (d, J=14) 3.01 (d, J=14)	2.00 (s)	1.00 (d, J=7.0)

Table 6. The NMR spectra of the acetates (XIVa and XIVb) in $CDCl_3$



	a	b	c	d	e
XIVa	1.25 (t, J=7.0)	4.10 (q, J=7.0)	2.86 (d, J=14) 3.32 (d, J=14)	1.99 (s)	0.90 (m)
XIVb	1.24 (t, J=7.0)	4.08 (q, J=7.0)	2.75 (d, J=14) 2.99 (d, J=14)	2.01 (s)	0.89 (t, J=5.0)

the major products (IIa and IXa) are observed as well-defined AB-type quartets in $CDCl_3$, while completely-collapsed singlets result in pyridine-d_5. On the other hand, the methylene protons of the minor products (IIb and IXb) in $CDCl_3$ are observed as a singlet and as a slightly separated quartet, respectively, which is also collapsed to a singlet in pyridine-d_5. All of the acetates show well-defined quartets arising from methylene protons alpha to the ethoxycarbonyl group in $CDCl_3$. Tables 3 and 4 report the Δ values[12] for the methyl and methylene protons present in the ethyl cyclohexylacetate derivatives obtained in this study. It is evident from the data presented in these tables that definite relationships exist between the chemical-shift values induced in pyridine (Δ values) and the location and orientation of solute protons. The methyl protons of the ester group experience shielding effects of 0.12—0.15 ppm in pyridine relative to chloroform, while those of methylene protons of the ester group are small, 0.03—0.06 ppm. Since the differences in these values due to the ester group of epimeric alcohols are very small, these shifts induced in pyridine have no value for conformational analysis. However, in IIa and IXa the Δ values observed for methylene protons alpha to the ethoxycarbonyl group are large ($\Delta = -0.22$ and -0.24 ppm respectively), while relatively small values are observed in IIb ($\Delta = -0.10$ ppm) and IXb ($\Delta = -0.10$ ppm). Therefore, these pyridine-induced shifts of the methylene protons of -CH_2CO_2R group seem to be useful for the conformational analysis. Furthermore, the $\delta_A - \delta_B$ values[13] which are summarized in Table 7 are also useful for this purpose, for the compounds (IIa, IXa, XIIIa, and XIVa) possessing an equatorial -CH_2CO_2R group have larger values than the compounds (IIb, IXb, XIIIb, and XIVb) possessing an axial -CH_2CO_2R group. The chemical shift of the hydroxyl proton also depends on its conformation. As may be seen in the IIa (3.07 ppm) and IXa (*ca.* 2.9 ppm) compounds, the axial hydroxyl protons show signals in a higher magnetic field than do those of equatorial hydroxyl protons (IIb: 3.64 ppm and IXb: 3.65 ppm).

Table 7. The $\delta_A - \delta_B$ values of methylene protons of CH_2CO_2R group in $CDCl_3$

-CH_2CO_2R (Hz)			
equatorial		axial	
IIa	23	IIb	0
IXa	26	IXb	6
XIIIa	29	XIIIb	16
XIVa	28	XIVb	14

From the above correlation between the Reformatsky and the Grignard reaction products, the results of the spectral analysis, and the chromatographic behavior, the configurations of the entering ester group relative to the alkyl group at the 2 position of the major products (IIa and IXa) in the Reformatsky reaction may be identified as *trans* configurations, while those of the minor products (IIb and IXb) are *cis*. Therefore, it is evident that the Reformatsky and the Grignard reaction with 2-alkylcyclohexanones proceed in a similar fashion; that is, the entering group predominantly approaches to the carbonyl group from the equatorial side, which derives to the axial hydroxyl compound.

The stereoselectivity of the Reformatsky reaction observed is slightly less than that of the Grignard reaction.

Experimental

All the melting and boiling points are uncorrected. The NMR spectra were taken on a Hitachi Model R-20 NMR spectrometer (60 MHz), using tetramethylsilane as the internal standard. Their chemical shifts are presented in terms of δ values; s: singlet; bs: broad singlet; d: doublet; t: triplet; q: quartet. The column chromatography was performed on Merck silica gel (0.08 mm).

Ethyl 2-Methyl-1-hydroxycyclohexylacetate (II). A solution of ethyl bromoacetate (12.5 g: 0.075 mol) in dry benzene (12.0 m*l*) was added, drop by drop at 80°C and over a period of 25 min, to a thoroughly stirred mixture of 2-methylcyclohexanone (5.6 g: 0.050 mol), purified zinc powder[14] (4.9 g: 0.075 mol), and dry benzene (6.0 m*l*). When the exothermic reaction started, the heating bath was removed, if neccessary; the temperature was kept at 80—87°C during the addition. After the addition was complete, the mixture was refluxed for 30 min, cooled, decomposed with dilute hydrochloric

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[12] Δ ppm=δ in $CDCl_3$−δ in pyridine-d_5.

[13] Calculated from the chemical shifts (AB-type quartets) of the methylene protons alpha to the ethoxycarbonyl group.

[14] R. L. Shriner, "Organic Reactions," Vol. 1, Wiley, New York (1942), p. 16.

acid (5%: 60 m*l*), and then extracted with ether. The ether extract was successively washed with water, a sodium hydrogencarbonate solution, and water, and then dried over sodium sulfate. The solvent was evaporated and the residue was distilled to give II as an oil; bp 119—122°C/10 mmHg; yield 8.4 g (84%). The other runs of this condensation are summarized in Table 1.

Separation of II into IIa and IIb. A 4.2×30 cm column was prepared from silica gel (200 g) suspended in purified benzene. To this was added the above sample (II: 2.520 g), after which elution with benzene containing 3% ether was carried out. Fractions 1—8 (800 m*l*) were discarded. Fractions 9—19 (550 m*l*) were evaporated to give IIa (2.035 g) as an oil.

Found: C, 65.87; H, 10.11%. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%.

Fraction 20 (50 m*l*) gave nothing. Fractions 21—36 (800 m*l*) were evaporated to give IIb (0.458 g) as an oil.

Found: C, 66.21; H, 9.82%. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%.

Hydrolysis of IIa and IIb. *a*) A mixture of IIa (1.00 g), aqueous sodium hydroxide (10%: 4.0 m*l*), and methanol (10 m*l*) was refluxed for 1.5 hr. After a usual work-up, the crude product was recrystallized from petroleum benzin containing a small amount of ether to give *trans*-2-methyl-1-hydroxycyclohexylacetic acid (IIIa) as colorless crystals; mp 78—79°C; yield 780 mg. A mixed-melting-point determination with IIIb (mp 80—81°C) showed 68—71°C. NMR in $CDCl_3$: 0.94 (3H, bs, $-C\underline{H}_3$), 2.36 and 2.77 (2H, each d and J=15 Hz, $-C\underline{H}_2CO_2H$), 6.80 (2H, bs, $-O\underline{H}$ and $-CO_2\underline{H}$). NMR in pyridine-d_5: 1.14 (3H, d, J=5.0 Hz, $-C\underline{H}_3$), 2.78 and 2.91 (2H, each d and J=14 Hz, $-C\underline{H}_2CO_2H$).

Found: C, 62.73; H, 9.55%. Calcd for $C_9\underline{H}_{16}O_3$: C, 62.76; H, 9.36%.

The *p*-bromophenacyl ester (IVa) was prepared from IIIa by a usual method. The crude product was recrystallized from aqueous methanol to give colorless crystals, mp 86—88°C, which gave a positive Beilstein halogen test.

Found: C, 55.12; H, 5.79%. Calcd for $C_{17}H_{21}O_4Br$: C, 55.29; H, 5.73%.

b) A mixture of aqueous sodium hydroxide (10%: 2.0 m*l*) and IIb (500 mg) in methanol (5.0 m*l*) was treated as has been described for IIIa; *cis*-2-methyl-1-hydroxycyclohexylacetic acid (IIIb) was thus obtained as colorless crystals; mp 80—81°C; yield 300 mg. NMR in $CDCl_3$: 0.94 (3H, d, J=7.0 Hz, $-C\underline{H}_3$), 2.53 (2H, s, $-C\underline{H}_2CO_2H$), 7.08 (2H, bs, $-O\underline{H}$ and $-CO_2\underline{H}$). NMR in pyridine-d_5: 1.05 (3H, d, J=6.5 Hz, $-C\underline{H}_3$), 2.72 (2H, s, $-C\underline{H}_2CO_2H$).

Found: C, 62.68; H, 9.51%. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36%.

The *p*-bromophenacyl ester (IVb), colorless crystals, mp 91.5—92.5°C, was prepared from IIIb by a usual method.

Found: C, 54.97; H, 5.84%. Calcd for $C_{17}H_{21}O_4Br$: C, 55.29; H, 5.73%.

Reduction of IIa and IIb with $LiAlH_4$. *a*) A solution of IIa (1.760 g) in dry ether (15 m*l*) was added, drop by drop and over a period of 50 min, to a suspension of $LiAlH_4$ (650 mg) in dry ether (15 m*l*) at room temperature, and then the mixture was gently refluxed for 2 hr. After a usual work-up, the crude product was recrystallized from petroleum benzin to give Va as colorless crystals; mp 67—68°C; yield 1.140 g (82%).

Found: C, 68.46; H, 11.63%. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47%.

b) The IIb ester (2.770 g) was reduced with $LiAlH_4$ (1.060 g) by a method similar to that used for Va. The diol, Vb, was thus obtained as an oil (2.060 g) which showed no carbonyl absorption band in its IR spectrum and which could be used for the next step without purification. For analysis it was purified by means of column chromatography on silica gel.

Found: C, 68.10; H, 11.68%. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47%.

cis- *and* trans-*2-Methyl-1-ethylcyclohexanols (VIIa and VIIb).* *a*) *From Va and Vb*: A mixture of Va (1.100 g) and *p*-toluenesulfonyl chloride (1.330 g) in dry pyridine (10 m*l*) was allowed to stand at room temperature for 30 hr and then poured into a mixture of ice and dilute hydrochloric acid (10%: 50 m*l*). The mixture was extracted with ether, and the extract was washed with water, dried over sodium sulfate, and then evaporated under a vacuum to give crude VIa as a yellow oil (1.284 g).

A solution of the above crude tosylate (VIa) in dry tetrahydrofuran (10 m*l*) was added, drop by drop and over a period of 10 min at room temperature, to a suspension of $LiAlH_4$ (500 mg) in dry tetrahydrofuran (10 m*l*); there after then the mixture was refluxed for 3 hr. After a usual work-up, the crude product was purified by means of chromatography on silica gel (70 g), after which elution with benzene containing 3% ether was carried out. Fractions 1—7 (350 m*l*) were discarded. Fractions 8—14 (175 m*l*) were evaporated to give VIIa (293 mg) as a colorless oil.

Found: C, 75.74; H, 12.71%. Calcd for $C_9H_{18}O$: C, 75.99; H, 12.76%.

When elution was continued with benzene containing 50% ether, the starting Va was recovered as colorless crystals (219 mg: mp 67—68°C).

By a method similar to that used for VIIa, the Vb diol (2.060 g) was tosylated with *p*-toluenesulfonyl chloride and then reduced with $LiAlH_4$ to give crude VIIb (1.359 g). When this was purified by means of chromatography on silica gel (150 g), pure VIIb (306 mg) was obtained as a colorless oil.

Found: C, 75.80; H, 12.68%. Calcd for $C_9H_{18}O$: C, 75.99; H, 12.76%.

The starting Vb (451 mg) was also recovered.

b) *From the Grignard Reaction*: 2-Methyl-1-ethylcyclohexanol (VII: bp 70—74°C/11 mmHg) was prepared in a 75% yield from I and ethylmagnesium iodide by the method of Cook and Laurence.[9] The product (2.078 g) was chromatographed on silica gel (200 g), after which elution with benzene containing 3% ether was carried out. The first (1.220 g) and second (0.115 g) fractions thus obtained were shown to be identical with the above VIIa and VIIb respectively by a spectral comparison.

Ethyl trans- *and* cis-*2-Ethyl-1-hydroxycyclohexylacetates (IXa and IXb).* A mixture of 2-ethylcyclohexanone (VIII: 5.00 g), purified zinc powder (3.90 g), and dry benzene (5.0 m*l*) was treated with a solution of ethyl bromoacetate (10.0 g) in dry benzene (10 m*l*) by a method similar to that used for II. The crude product was distilled under a vacuum to give a colorless oil (7.10 g: bp 137—141°C/14 mmHg) in an 83% yield.

The above ester (2.190 g) was chromatographed on silica gel (200 g), after which elution with benzene containing 3% ether was carried out. Fractions 1—18 (900 m*l*) were discarded. Fractions 19—25 (350 m*l*) were evaporated to give *trans*-2-ethyl-1-hydroxycyclohexylacetate (IXa: 1.687 g) as a colorless oil.

Found: C, 67.06; H, 10.43%. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35%.

Fraction 26 (50 m*l*) was evaporated to give a colorless oil (0.105 g) which was shown to be a mixture (*ca.* 1:1) of IXa and IXb by IR and NMR analyses. Fractions 27—36 (500 m*l*) were evaporated to give *cis*-2-ethyl-1-hydroxycyclohexylacetate (IXb: 0.386 g) as colorless crystals; mp 50.5—51.5°C.

Found: C, 67.05; H, 10.42%. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35%.

Reduction of IXa and IXb with $LiAlH_4$. *a*) The IXa ester (1.280 g) was reduced with $LiAlH_4$ (0.450 g) by a method similar to that used for Va. The product was recrystallized from petroleum benzin containing a small amount of ether to give Xa as colorless crystals; mp 93.5—94.5°C; yield, 0.850 g.

Found: C, 69.68; H, 11.83%. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70%.

b) The IXb ester (0.720 g) was also reduced with $LiAlH_4$ to give Xb as colorless crystals; mp 73—73.5°C; yield, 0.400 g.

Found: C, 69.66; H, 11.83%. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70%.

cis- *and* trans-*1,2-Diethylcyclohexanols (XIIa and XIIb).* *a*) *From Xa and Xb*: By a method similar to that used for VIIa, the Xa diol (350 mg) was tosylated and then reduced to give crude XIIa (280 mg), which was subsequently chromatographed on silica gel (30 g) to give pure XIIa (161 mg) as a colorless oil.

Found: C, 76.69; H, 12.93%. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90%.

XIIb was also obtained from Xb by a method similar to that used for XIIa.

Found: C, 76.82; H, 12.88%. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90%.

b) *From the Grignard Reaction*: 1,2-Diethylcyclohexanol was prepared by the method of Dice *et al.*[10] This (2.300 g) was chromatographed on silica gel (200 g), after which elution with benzene containing 3% ether was carried out. The first (1.753 g) and second (0.123 g) fractions obtained were shown to be identical with XIIa and XIIb respectively by a spectral comparison.

The Acetates (*XIIIa, XIIIb, XIVa and XIVb*). *a*) A mixture of IIa (930 mg), *p*-toluenesulfonic acid monohydrate (50 mg), isopropenyl acetate (2.0 m*l*), and dry toluene (10 m*l*) was refluxed for 3 hr; then the solvent was slowly distilled off over a period of 60 min to *ca.* 5 m*l*. To the cold solution solid sodium hydrogencarbonate (200 mg) was added, and, after stirring for 10 min, the mixture was filtered. The filtrate was evaporated under a vacuum, and the residue was purified by chromatography to give XIIIa as a colorless oil; yield, 1.105 g.

Found: C, 64.58; H, 9.26%. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15%.

b) The other acetates (XIIIb, XIVa, and XIVb) were also prepared in an almost quantitative yield by a method similar to that used for XIIIa.

XIIIb, Found: C, 64.27; H, 9.21%. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15%.

XIVa, Found: C, 65.61; H, 9.56%. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44%.

XIVb, Found: C, 65.53; H, 9.51%. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44%.