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The Stereochemistry of Nucleophilic Addition. IV.[1] The Condensation of 2,2,6-Trimethylcyclohexanone with *t*-Butyl Acetate in the Presence of Lithium Amide

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The stereochemistry of the condensations of 2,2,6-trimethylcyclohexanone with *t*-butyl acetate in the presence of lithium amide, with ethyl bromoacetate in the presence of zinc (Reformatsky reaction), and with ethylmagnesium iodide (Grignard reaction) was studied. The configurations of the products in these reactions were assigned on the basis of their chromatographic behavior, and on the basis of spectroscopic and chemical studies of them. From the present experiments it is evident that all of these nucleophilic addition reactions proceed in a similar fashion. Further, the treatment of *t*-butyl 1-hydroxy-2,2,*t*-6-trimethyl-*r*-1-cyclohexaneacetate (IIa) with potassium hydrogensulfate or with dilute sulfuric acid gave (±)-*cis*-tetrahydroactinidiolide (IX), which was isolated from the essential oil of cigar tobacco leaves by Kaneko and Hoshino, while the treatment of IIa with isopropenyl acetate in the presence of *p*-toluenesulfonic acid gave a mixture of IX and its *trans*-isomer (X).

In previous papers,[1-3] the present authors have reported on the stereochemistry of the Reformatsky reaction with carbonyl compounds possessing an asymmetic α-carbon atom. A similar aldol-type condensation of *t*-butyl acetate with carbonyl compounds in the presense of lithium amide has been reported by Hauser *et al.*[4,5] However, since this reaction has not been studied stereochemically, it is of interest to study the stereochemistry of the aldol-type condensation with carbonyl compounds possessing an asymmetric α-carbon atom, and to compare it with that of the Reformatsky and Grignard reactions. The present paper will describe the stereochemistry of these nucleophilic addition reactions with 2,2,6-trimethylcyclohexanone (I). The condensation of I with *t*-butyl acetate in ether in the presence of lithium amide gave a mixture of epimeric *t*-butyl 1-hydroxy-2,2,6-trimethyl-1-cyclohexaneacetates (IIa and IIb) in a 76% yield, accompanied by a small amount of dehydrated esters (3% yield, IIIa and IIIb). The separation of these esters was successively carried out by means of column chromatography on silica gel to give, in the order of elution, the oily IIIa, IIIb, IIa, and IIb esters in a 3 : 1 : 78 : 18 ratio. The structures of IIIa and IIIb were assigned on the basis of their spectral data, as will be shown in the Experimental section. The alkaline hydrolyses of IIa and IIb gave the corresponding crystalline β-hydroxy acids, IVa (mp 118.5—119.5°C) and IVb (mp 143.5—144°C) respectively. Sakan *et al.*[6], during the course of their synthetic work on dihydroactinidiolide, reported on the synthesis of ethyl 1-hydroxy-2,2,6-trimethyl-1-cyclohexaneacetate (V) by the Reformatsky reaction of I with ethyl bromoacetate, but the composition of the epimeric alcohols expected was not recorded. Therefore, the stereochemistry of this reaction was also studied in order to compare it with that of the above aldol-type condensation. A mixture of the epimeric β-hydroxy esters obtained (62% yield) by the Reformatsky reaction was also separated by means of column chromatography on silica gel into two oily ethyl esters

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[1] Part III. T. Matsumoto, Y. Tachibana, T. Ohno, and K. Fukui, *J. Sci. Hiroshima Univ., Ser., A*. **35**, 231 (1971). Although the formulas depicted represent only one enantiomer, they are taken to indicate a racemate.

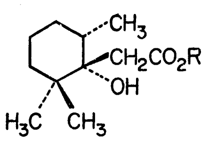
[2] T. Matsumoto and K. Fukui, This Bulletin, **44**, 1090 (1971).

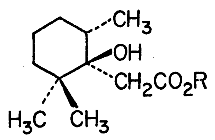
[3] T. Matsumoto, I. Tanaka, and K. Fukui, *ibid.*, **44**, 3378 (1971).

[4] C. R. Hauser and W. H. Puterbaugh, *J. Amer. Chem. Soc.*, **73**, 2972 (1951); **75**, 1068, 4756 (1953).

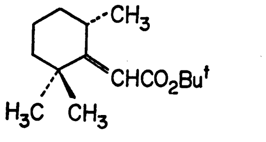
[5] C. R. Hauser and W. R. Dunnavant, *J. Org. Chem.*, **25**, 1296 (1960).

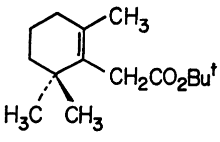
[6] T. Sakan, S. Isoe, and S. Be Hyeon, *Tetrahedron Lett.*, **1967**, 1623.



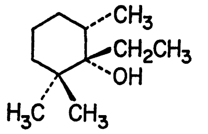


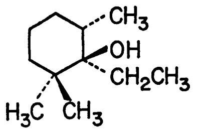
IIa R=Bu^t IIb
IVa R=H IVb
Va R=Et Vb



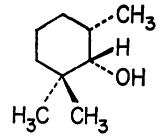


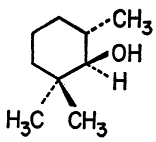
IIIa IIIb



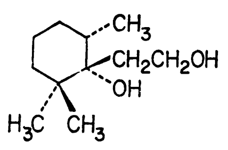


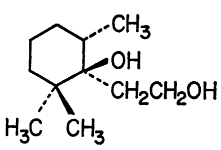
VIa VIb





VIIa VIIb





VIIIa VIIIb

(Va and Vb) in a 76 : 24 ratio. These major (Va) and minor (Vb) esters were hydrolyzed with sodium hydroxide in methanol to give the corresponding acids (mp 117—119°C and mp 143—144°C), which were identified as IVa and IVb respectively. This finding means that the two reactions proceed on similar stereochemical courses. The NMR spectra of IIa, IIb, Va, and Vb are summarized in Tables 1 and 2. As is shown in these tables, the methylene protons alpha to the ester group in the major alcohols (IIa and Va) are observed as well-defined AB-type quartets in $CDCl_3$, while those in the minor alcohols (IIb and Vb) are observed as singlets. The pyridine-induced solvent shifts (Δ values[7]) of these methylene protons in IIa (-0.17 ppm) and Va (-0.13 ppm) are slightly larger than those in the corresponding epimers (IIb: -0.13 ppm and Vb: -0.08 ppm), although the differences (II: 0.04 ppm and V: 0.05 ppm) of these Δ values between the epimeric alcohols are smaller than those (0.10—0.14 ppm) in the cases of 2-monoalkylcyclohexylacetate derivatives which have been reported in previous papers[1,2] The above NMR spectral data suggest that the orientations of the $-CH_2CO_2R$ groups in the major (IIa and Va) and minor (IIb and Vb) alcohols are equatorial and axial respectively. These assignments are also supported by their IR spectra, because IIa and Va show the characteristic hydroxyl absorption bands, at 983 and 985 cm^{-1}, respectively, which suggest the presence of axial hydroxyl groups; on the other hand, in the cases of IIb and Vb their spectra (IIb: 1060 cm^{-1} and Vb: 1060 cm^{-1}) suggest the presence of equatorial hydroxyl groups. Recently, Demarco *et al.*[8] reported on the pyridine-induced solvent shift of a methyl group vicinally situated to a hydroxyl group; the extent of the deshielding is dependent upon the magnitude of the dihedral angle, θ,[9] subtended between the methyl and hydroxyl groups. As may be seen from Tables 1 and 2, the pyridine-induced solvent shifts[10] of the methyl groups at the 2 and 6 positions are observed to be in good accordance with the results of Demarco *et al.* That is, in the major alcohols (IIa and Va) one of three methyl groups is only slightly shifted in pyridine-d_5 (0.01—0.03 ppm), whereas the two other methyl groups experience strong deshielding effects (0.14—0.19 ppm). These pyridine-induced solvent shifts strongly suggest the presence of an axial hydroxyl, an axial methyl, and two equatorial methyl groups in IIa and Va. On the other hand, in the minor alcohols (IIb and Vb) all of the three methyl groups situated on the cyclohexane ring are shifted (0.10—0.13 ppm) in pyridine-d_5; this suggests the presence of an equatorial hydroxyl, an axial methyl, and two equatorial methyl groups.

Subsequently, the stereochemistry of the Grignard reaction of I with ethylmagnesium iodide in ether was also studied in order to compare it with that of the above aldol-type condensation and that of the Reformatsky reactions. The crude product obtained was then purified by means of column chromatography to give the epimeric alcohols (VIa and VIb) in a 58 : 42 ratio, accompanied by two by-products (VIIa and VIIb) in a 34 : 66 ratio.[11] The structures of VIIa (mp 62.5—63.5°C) and VIIb (mp 49—50°C) were confirmed by direct comparisons with the authentic 2,2,*c*-6- and 2,2,*t*-6-trimethyl-*r*-1-cyclohexanols[12] which had been prepared by the reduction of I with $LiAlH_4$ in ether, followed by the separation of a mixture of the epimers (30 : 70 ratio[11]) by means of column chromatography. The NMR spectra of VIIa and VIIb are summarized in Table 3; the preferred conformations of these alcohols may be assigned as

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[7] $\Delta_{ppm}=\delta$ in $CDCl_3-\delta$ in pyridine-d_5.

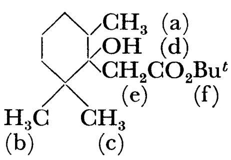
[8] P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

[9] As θ decreases in magnitude, the Δ values increase; that is, when θ is 180°, 85°, and 60°, the reported Δ values are -0.03, -0.13, and -0.20— -0.27 ppm respectively.

[10] The values observed in this series were somewhat smaller than those of Demarco *et al.*[8] See also Ref. 2.

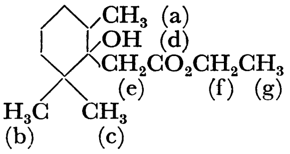
[11] Since VIIa and VIIb were easily sublimed during the evaporation of the solvent, the ratio was obtained by a NMR spectral analysis of the crude product.

TABLE 1. THE NMR SPECTRA OF IIa AND IIb



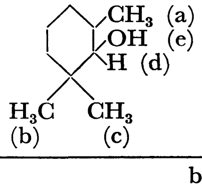
		a	b	c	d	e	f
IIa	$CDCl_3$	0.85 (d, J=6 Hz)	0.91 (s)	0.94 (s)	4.65 (s)	2.26 (d, J=16 Hz) 2.49 (d, J=16 Hz)	1.48 (s)
	Py-d_5	1.02 (d, J=6 Hz)	1.10 (s)	0.97 (s)	—	2.45 (d, J=16 Hz) 2.65 (d, J=16 Hz)	1.45 (s)
	Δ7)	−0.17	−0.19	−0.03	—	−0.17	+0.03
IIb	$CDCl_3$	0.91 (d, J=6.5 Hz)	0.91 (s)	1.04 (s)	5.15 (s)	2.44 (s)	1.48 (s)
	Py-d_5	1.01 (d, J=6.5 Hz)	1.02 (s)	1.15 (s)	—	2.57 (s)	1.47 (s)
	Δ7)	−0.10	−0.11	−0.11	—	−0.13	+0.01

TABLE 2. THE NMR SPECTRA OF Va AND Vb



		a	b	c	d	e	f	g
Va	$CDCl_3$	0.85 (d, J=6 Hz)	0.93 (s)	0.93 (s)	4.31 (s)	2.37 (d, J=16 Hz) 2.54 (d, J=16 Hz)	4.14 (q, J=7 Hz)	1.26 (t, J=7 Hz)
	Py-d_5	1.01 (d, J=8 Hz)	1.07 (s)	0.94 (s)	—	2.59 (s)	4.09 (q, J=7 Hz)	1.15 (t, J=7 Hz)
	Δ7)	−0.16	−0.14	−0.01	—	−0.13	+0.05	+0.11
Vb	$CDCl_3$	0.90 (d, J=6 Hz)	0.88 (s)	1.04 (s)	4.84 (bs)	2.51 (s)	4.14 (q, J=7 Hz)	1.27 (t, J=7 Hz)
	Py-d_5	1.02 (d, J=6 Hz)	1.01 (s)	1.16 (s)	—	2.59 (s)	4.12 (q, J=7 Hz)	1.16 (t, J=7 Hz)
	Δ7)	−0.12	−0.13	−0.12	—	−0.08	+0.02	+0.11

TABLE 3. THE NMR SPECTRA OF VIIa AND VIIb

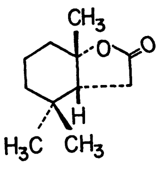


		a	b	c	d	e
VIIa	$CDCl_3$	0.93 (d, J=6.5 Hz)	0.96 (s)	0.91 (s)	3.15 (bs)	1.39 (s)
	Py-d_5	1.09 (d, J=6.5 Hz)	1.14 (s)	0.93 (s)	3.28 (bs)	—
	Δ7)	−0.16	−0.18	−0.02	−0.13	—
VIIb	$CDCl_3$	0.98 (d, J=5 Hz)	0.98 (s)	0.88 (s)	2.83 (d, J=9 Hz)	1.44 (s)
	Py-d_5	1.13 (d, J=7 Hz)	1.14 (s)	1.07 (s)	2.95 (d, J=9 Hz)	—
	Δ7)	−0.15	−0.16	−0.19	−0.12	—

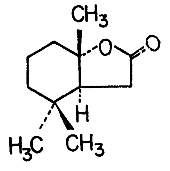
follows. The magnitude of the coupling constant between the protons at the 1 and 6 positions suggests that the orientations of these vicinal protons in VIIa and VIIb are equatorial-axial[13] and diaxial respectively. The pyridine-induced solvent shifts of the methyl groups also suggest that the orientations of the hydroxyl groups in VIIa and VIIb are axial and equatorial respectively. Subsequently, the correlation of the β-hydroxy esters (II and V) with the alcohols (VIa and VIb) was also carried out in the following manner. The reduction of IIa and Va with $LiAlH_4$ in ether gave the same VIIIa diol (mp 46—46.5°C). On the other hand, the VIIIb diol (mp 51.5—52.5°C) was also obtained by the similar reduction of IIb or Vb. The VIIIa and VIIIb diols were subjected to tosylation with *p*-toluenesulfonyl chloride in pyridine; the reduction of the resulting tosylates with $LiAlH_4$ in tetrahydrofuran gave 1-ethyl-2,2,*c*-6-trimethyl-*r*-1-cyclohexanol and its *t*-6-isomer, which were shown to be identical with VIa and VIb respectively by comparisons of their IR and NMR spectra.

From the present study, it is evident that all of the aldol-type condensation and the Reformatsky reaction and the Grignard reaction with I proceed in a similar fashion. Furthermore, it is well known[2,14] that isomers with equatorial hydroxyl groups can be expected to be adsorbed more strongly on chromatography and that, therefore, they can be expected to be more difficult to elute than the isomers with more hindered axial hydroxyls. In this study, the isomers (IIa, Va, VIa, and VIIa) were eluted first in each instance on column chromatography. This behavior also supports the presence of the axial hydroxyl groups in these alcohols.

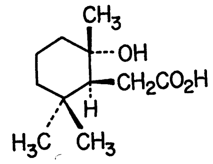
Finally, the tre2tment of IIa with potassium hydrogensulfate at 210—226°C or with dilute sulfuric acid under refluxing afforded a γ-lactone (mp 79.5—80.5°C). From the physical and spectral data which are shown in the Experimental section, the structure of the above lactone was deduced to be (±)-*cis*-tetrahydroactinidiolide (IX). The preparation of the optically-active or inactive IX by different methods had already been reported by Sakan *et al.*[6] and by other workers.[15–19] On the other hand, the treatment of IIa in toluene with isopropenyl acetate in the presence of *p*-toluenesulfonic acid gave a mixture of γ-lactones; the components were successfully separated by means of column chromatography on silica gel to give IX and a *trans*-γ-lactone (X), mp 71.5—74.5°C. The NMR spectrum of X in $CDCl_3$ showed signals at δ 0.92, 0.95, and 1.32 ppm due to three methyl groups. In contrast with the *cis*-lactone (IX), the lactone X was easily hydrolyzed with methanolic sodium hydroxide to give the corresponding γ-hydroxy acid (XI), mp 105—107°C; the preparation of this substance by a different method had also been reported by Ohloff and Schade.[15]



IX



X



XI

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).

The Condensation of 2,2,6-Trimethylcyclohexanone (I) with t-Butyl Acetate. A solution of *t*-butyl acetate (49.5 g: 0.426 mol) in dry ether (45 m*l*) was stirred, drop by drop over a 15-min period, into a lithium amide solution which had been freshly prepared from lithium (2.96 g: 0.423 mol) and liquid ammonia (*ca.* 150 m*l*), with cooling in a dry ice–acetone bath. After the ammonia had evaporated, the residual syrup was diluted with dry ether (60 m*l*). To this solution there was then added, drop by drop, a solution of I[20] (15 g: 0.017 mol) in dry ether (30 m*l*) at room temperature over a 20-min period. The mixture was refluxed for 60 min, cooled, decomposed with dilute hydrochloric acid (3 N: 30 m*l*), and then extracted with ether. The extract was successively washed with aqueous sodium hydrogencarbonate (10%) and water, and then dried over sodium sulfate. After the removal of the solvent, the residue was distilled under a vacuum to give an oil (28.5 g); bp 123—148°C/14 mmHg. A part (4.00 g) of the above distilled oil was chromatographed on silica gel (200 g), using benzene as the eluent. The first fraction gave an oil (IIIa; 73 mg) which showed no hydroxyl absorption band in its IR spectrum. IR in $CHCl_3$: 1696 (C=O), 1622 cm^{-1} (C=C). NMR

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[12] G. Barraud, R. Cornubert, and A. M. Lemoine-Tressont, *Bull. Soc. Chim. Fr.*, **1957**, 1499. These authors had prepared VIIa (mp 61—62°C) and VIIb (mp 54°C) from I by catalytic hydrogenation in the presence of platinum and by reduction with sodium in ethanol respectively.

[13] The possibility of its being diequatorial is rejected on the basis of the result of the pyridine-induced solvent shift of the methyl group at the 6 position.

[14] S. Winstein and N. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

[15] G. Ohloff and G. Schade, *Chem. Ber.*, **91**, 2017 (1958).

[16] W. C. Bailey, Jr., A. K. Bose, R. M. Ikeda, R. H. Newman, H. V. Secor, and C. Varsel, *J. Org. Chem.*, **33**, 2819 (1968).

[17] E. Demole and P. Enggist, *Helv. Chim. Acta*, **51**, 481 (1968).

[18] M. Ribi and C. H. Eugster, *ibid.*, **52**, 1732 (1969).

[19] H. Kaneko and K. Hoshino, *Agr. Biol. Chem. (Jap.)*, **33**, 969 (1969). The above authors had reported the isolation of tetrahydroactinidiolide from the essential oil of cigar tabacco leaves. The reported IR spectrum of the natural sample is identical with that of the synthetic (±)-IX.

[20] C. L. Stevens and A. J. Weinheimer, *J. Amer. Chem. Soc.*, **80**, 4072 (1958).

in $CDCl_3$: 1.10 and 1.16 (each 3H and s, 2-$C\underline{H}_3$), 1.24 (3H, d, $J=7$ Hz, $-\overset{|}{C}HC\underline{H}_3$), 1.47 (9H, s, $-C(C\underline{H}_3)_3$), 5.65 (1H, s, $-\overset{|}{C}=C\underline{H}CO_2Bu^t$). UV: λ_{max}^{EtOH} 223 nm ($\varepsilon=11900$).

Found: C, 75.59; H, 11.02%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%.

The hydrolysis of IIIa in ethanol with aqueous sodium hydroxide gave the corresponding acid as colorless crystals; mp 101—102°C (from ether containing petroleum ether). IR in $CHCl_3$: 1680 (CO_2H), 1620 cm^{-1} (C=C).

Found: C, 72.53; H, 10.12%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

The second fraction gave an oil (IIIb: 35 mg) which also showed no hydroxyl absorption band in its IR spectrum and no absorption maximum in the 210—250 nm region of its UV spectrum. IR in $CHCl_3$: 1725 cm^{-1} (C=O). NMR in CCl_4: 0.96 (6H, s, 2-$C\underline{H}_3$), 1.42 (9H, s, $-C(C\underline{H}_3)_3$), 1.57 or 1.46 (3H, s, $-\overset{|}{C}=\overset{|}{C}C\underline{H}_3$), 2.88 (2H, s, $-C\underline{H}_2CO_2Bu^t$).

Found: C, 75.46; H, 11.14%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%.

The third fraction gave IIa as an oil (2.364 g). IR in $CHCl_3$: 3450 (OH), 1702 cm^{-1} (C=O).

Found: C, 70.11; H, 10.89%. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01%.

Further elution was carried out with benzene containing 3% ether; the fourth fraction gave IIb as an oil (0.550 g). IR in $CHCl_3$: 3440 (OH), 1702 cm^{-1} (C=O).

Found: C, 70.39; H, 11.01%. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01%.

The Reformatsky Reaction of I with Ethyl Bromoacetate. A solution of ethyl bromoacetate (16.0 g: 0.092 mol) in dry benzene (15 m*l*) was stirred; drop by drop at 85—88°C, into a mixture of I (6.50 g: 0.046 mol), purified zinc powder[21] (6.40 g: 0.092 mol), and dry benzene (2.0 m*l*). After the addition was complete, the mixture was refluxed for 30 min and then treated in the usual manner. The crude product was distilled under a vacuum to give an oil; bp 137—138°C/10 mmHg; yield, 7.0 g. A part (1.520 g) of the above oil was chromatographed on silica gel (100 g), using benzene as the eluent. The first fraction gave a dehydrated ester (10 mg). The second fraction gave Va as an oil (1.006 g).

Found: C, 68.52; H, 10.65%. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59%.

The third fraction gave Vb as an oil (0.333 g).

Found: C, 68.46; H, 10.43%. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59%.

*1-Hydroxy-2,2,*t*-6-trimethyl-*r*-1-cyclohexaneacetic Acid (IVa) and Its* c*-6-Isomer (IVb).* *a*) The hydrolysis of Va (1.00 g) in methanol with aqueous sodium hydroxide for 2 hr gave IVa as colorless crystals; mp 118.5—119.5°C; yield, 0.570 g. NMR in $CDCl_3$: 0.90 (3H, d, $J=5$ Hz $-\overset{|}{C}HC\underline{H}_3$), 0.98 (6H, s, 2-$C\underline{H}_3$), 2.47 and 2.67 (2H, each d and $J=16$ Hz, $-C\underline{H}_2CO_2H$).

Found: C, 65.89; H, 10.09%. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%.

Similarly, IIa was also hydrolyzed with aqueous sodium hydroxide for 5 hr to give IVa; mp 118.5—119.5°C.

b) The Vb ester (295 mg) was treated by a method similar to that used for IVa. The product (260 mg) was recrystallized from ether containing petroleum ether to give IVb as colorless crystals; mp 143.5—144°C; yield, 150 mg. NMR in $CDCl_3$: 0.96 (3H, d, $J=6.5$ Hz, $-\overset{|}{C}HC\underline{H}_3$), 0.98 and 1.06 (each 3H and s, 2-$\underset{|}{\overset{|}{C}}C\underline{H}_3$), 2.65 (2H, s, $-C\underline{H}_2CO_2H$).

Found: C, 66.16; H, 10.01%. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%.

Similarly, IIb was hydrolyzed to give IVb; mp 143.5—144°C.

Reduction of I with $LiAlH_4$. A solution of I (1.25 g) in dry ether (10 m*l*) was stirred, drop by drop over 20 min and at room temperature, into a suspension of $LiAlH_4$ (500 mg) in dry ether (10 m*l*). The mixture was refluxed for 3 hr, cooled, poured into a mixture of ice and dilute hydrochloric acid (10%: 25 m*l*), and then extracted with ether. The extract was washed with a saturated sodium chloride solution, dried over sodium sulfate, and then evaporated under a vacuum to give an oil (1.20 g) which showed no carbonyl absorption band in its IR spectrum. The NMR spectrum of the crude oil showed the presence of epimeric alcohols in a 30 : 70 ratio. The crude oil was chromatographed on silica gel (90 g), using benzene as the eluent. The first fraction gave VIIa[22] (327 mg), which was recrystallized from ether containing petroleum ether to give colorless crystals; mp 62.5—63.5°C (lit,[12] mp 61—62°C): Found: C, 75.91; H, 12.73%.

The second fraction gave VIIb[22] (502 mg) as colorless crystals, mp 49—50°C (lit,[12] mp 54°C): Found: C, 75.84; H, 12.80%. A mixed fusion with VIIa showed *ca.* 25°C.

The Grignard Reaction of I with Ethylmagnesium Iodide. A solution of I (1.400 g) in dry ether (5.0 m*l*) was added, drop by drop over 15 min at room temperature, to the Grignard reagent which had been prepared from magnesium (360 mg) and ethyl iodide (2.600 g) in dry ether (7.0 m*l*). The mixture was refluxed for 4 hr, allowed to stand overnight at room temperature, and then worked up in a usual manner to give a crude product which showed the presence of VIIa and VIIb in a 34 : 66 ratio upon NMR spectrum analysis. The crude product was purified by means of column chromatography on silica gel (150 g). Elution was carried out with benzene to give four fractions. The first fraction gave VIa (401 mg) as an oil.

Found: C, 77.51; H, 13.11%. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02%.

The second fraction gave VIb (290 mg) as an oil.

Found: C, 77.63; H, 13.09%. Calcd for $C_{11}H_{22}O$; C, 77.58; H, 13.02%.

The third fraction gave colorless crystals (139 mg.[22] mp 62.5—63.5°C),which were shown to be identical with authentic VIIa by a mixed-melting-point determination and by a comparison of their spectra.

The fourth fraction gave colorless crystals (236 mg:[22] mp 49—50°C) which were also shown to be identical with authentic VIIb by a comparison of their IR spectra.

Reduction of IIa, IIb, Va, and Vb with $LiAlH_4$. *a) From IIa and Va:* A solution of IIa (1.550 g) in dry ether (20 m*l*) was reduced with $LiAlH_4$ (500 mg). The crude product (1.402 g) was purified by means of column chromatography on silica gel (70 g), using benzene containing 20% ether as the eluent. The first fraction gave the recovered IIa (673 mg). The second fraction gave a diol (VIIIa: 737 mg), which was then recrystallized from ether containing petroleum ether to give colorless crystals; mp 46—46.5°C.

Found: C, 71.08; H, 12.10%. Calcd for $C_{11}H_{22}O_2$:

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[21] R. L. Shriner, "Organic Reactions," Coll. Vol. I, p. 16 (1942).

[22] A part of the substance was lost by sublimation during the removal of the benzene.

C, 70.92; H, 11.90%.

Similarly, the ethyl ester (Va: 1.500 g) was also reduced with $LiAlH_4$ (500 mg) to give VIIIa (889 mg: mp 46—46.5°C).

b) *From IIb and Vb*: The esters (IIb and Vb) were also both reduced with $LiAlH_4$ to give VIIIb; mp 51.5—52.5°C. A mixed-melting-point determination with VIIIa showed 32—34°C.

Found: C, 71.14; H, 12.01%. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90%.

*1-Ethyl-2,2,*c*-6-(VIa) and 1-Ethyl-2,2,*t*-6-trimethyl-*r*-1-cyclohexanol (VIb).* *a*) A solution of VIIIa (400 mg), *p*-toluenesulfonyl chloride (440 mg), and dry pyridine (3.0 m*l*) was allowed to stand at room temperature for 60 hr. After a usual work-up, the crude product (420 mg) was dissolved in dry tetrahydrofuran (11.0 m*l*) and then reduced with $LiAlH_4$ (300 mg) for 3.5 hr under refluxing. The product was chromatographed on silica gel (40 g), using benzene containing 10% ether as the eluent. The first fraction gave an oil (126 mg) which was shown to be identical with VIa by a comparison of their IR spectra. The second fraction gave the recovered VIIIa (230 mg).

b) The diol VIIIb (573 mg) was treated by a method similar to that described in *a*) to give an oil (163 mg) which was identical with VIb. The starting VIIIb (253 mg) was also recovered.

2-Hydroxy-2,6,6-trimethyl-1-cyclohexaneacetic Acid γ-Lactones (IX and X). *a*) A mixture of IIa (3.40 g) and fused potassium hydrogensulfate (3.0 g) was heated at 210—226°C for 30 min in an oil bath. After cooling and the subsequent addition of water, the mixture was extracted with ether; the extract was washed with water, dried over sodium sulfate, and then evaporated. The crude product (2.04 g) was chromatographed on silica gel (200 g), using benzene containing 10% ether as the eluent, to give a *cis*-γ-lactone (IX: 1.66 g) ((±)-tetrahydroactinidiolide), which was then recrystallized from ether containing petroleum ether to give colorless crystals; mp 79.5—80.5°C (lit,[17] mp 77—79°C); Found: C, 72.25; H, 10.05%. The IR and NMR spectra of IX were in good accrodance with those in the literature.[6,16—18]

A mixture of the above *cis*-lactone (IX: 1.10 g) and aqueous sodium hydroxide (5%: 20 m*l*) was stirred and heated on a steam bath for 1 hr. The clear solution, after cooling, was acidified with dilute sulfuric acid to give the starting IX (0.95 g).

b) A mixture of IIa (429 mg) and dilute sulfuric acid 30%: 8.0 m*l*) was refluxed for 3 hr. After a usual work-up, the crude product (297 mg) was chromatographed on silica gel (25 g), using benzene containing 3% ether as the eluent, to give the *cis*-lactone (IX: 256 mg).

c) A mixture of IIa (635 mg), isopropenyl acetate (1.0 m*l*), and *p*-toluenesulfonic acid (40 mg) in dry toluene (12 m*l*) was refluxed for 3 hr, and then, after cooling, solid sodium hydrogencarbonate (140 mg) was added. The mixture was stirred at room temperature for 10 min and filtered; the filtrate was then evaporated under a vacuum to give a crude product which was chromatographed on silica gel (60 g). Elution was carried out with benzene containing 3% ether. The first fraction gave a *trans*-γ-lactone (X: 70 mg) which was recrystallized from ether containing petroleum ether to give colorless crystals; mp 71—74.5°C (softened at 66°C). A mixed-melting-point determination with the *cis*-γ-lactone (IX: mp 79.5—80.5°C) showed 50—55°C; it softened at room temperature.

Found: C, 72.63; H, 10.22%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

The second fraction gave the *cis*-γ-lactone (IX: 33 mg), the identity of which was established by an IR spectral comparison.

Hydrolysis of trans-γ-Lactone (X) with Alkali. A solution of X (50 mg) and aqueous sodium hydroxide (5%; 1.0 m*l*) in methanol (5.0 m*l*) was refluxed for 1 hr. After a usual work-up, the crude product was recrystallized from ether containing petroleum ether to give an acid (XI) as colorless crystals; mp 105—107°C (lit,[15] mp 113—115.5°C); Found: C, 66.16; H, 10.31%; yield, 40 mg. NMR in $CDCl_3$: 0.81 and 0.94 (each 3H and s, $-\overset{|}{\mathrm{C}}(\mathrm{C\underline{H}_3})_2$), 1.19 (3H, s, $-\overset{|}{\mathrm{C}}(\mathrm{OH})\mathrm{C\underline{H}_3}$), *ca.* 6.0 (2H, bs, $-\mathrm{CO_2\underline{H}}$ and $-\mathrm{O\underline{H}}$).