*Stereoisomers of 2,3-Camphane Diols**

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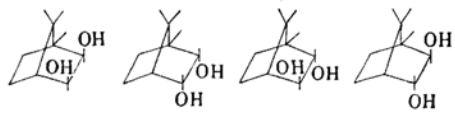
There should exist four possible diastereoisomeric camphane-2,3-diols, which in spite of having been prepared by several authors[1], were mostly obtained as mixtures of isomers, with its single epimer believed to have been isolated in fairly pure state by Rupe and Thommen[2]. Therefore, conformation of each epimer has not been established at all. Only Kwart and Gatos[3,4] recently assigned the structure to the one isomer of the Rupe and Thommen diol with positive evidence of infrared spectra and complex formation. It became then the purpose in these studies to isolate all theoretically possible diols and assign conformation; and, if possible, to correlate the isomeric composition of the diols prepared by various methods with the mode of reaction. Several facts which have been clarified are presented in this report. As the authors have hitherto studied *endo-* and *exo-* isomers of borneols and their epimerization[5,6], the hydrogenation of camphorquinone was similarly followed.

Synthesis of Four Stereoisomers.—Four epimers, namely *exo-exo-* (I), *endo-endo-* (II), *endo-exo-* (III), and *exo-endo-* (IV) may possibly result by reduction of camphorquinone. Effective isolation of pure



I II III IV

Fig. 1. Stereoisomers of 2,3-camphane diols.

* Partly presented at the Symposium on Terpenes, Kinki Univ., Nov. 30, 1957.

1) O. Mannase, *Ber.*, **30**, 659 (1897); ibid., **35**, 3811 (1902).

2) H. Rupe and W. Thommen, *Hev. Chim. Acta*, **30**, 933 (1947).

3) H. Kwart and G. C. Gatos, *J. Am. Chem. Soc.*, **80**, 881 (1958). The present author is indebted to Dr. H. Kwart for his kind advice and suggestion, and to Dr. S. J. Angyal for his unpublished reslut.

4) S. J. Angyal recently isolated four diols in fairly pure state. (A. C. S. Meeting, Sept., 1957, New York).

5) T. Takeshita and M. Kitajima, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **78**, 994 (1957).

6) T. Takeshita and M. Kitajima, ibid., **79**, 1468 (1958).

TABLE I. INFRARED SPECTA OF *cis*-DIOLS

	Free	Int.	Intra	Int.	Inter	Int.	$\Delta\nu$	OH-O[8]	Ratio (%)	Assignment
I	3630	0.151	3540	0.270	3380	0.440	90	1.5 Å	291.4	*exo-exo-*
II	3630	0.127	3535	0.300	3385	0.529	95	1.5 Å	416.5	*endo-endo-*

Concn. 20.0 mg./ml. CS_2; Cell length 0.5 mm. Free Int., Intra Int. and Inter Int. are peak intensity at free, intra-molecular and inter-molecular O–H stretching.
Ratio Inter, Int./Free, Int.

isomers can be achieved by selecting the procedure yielding the least number of components, and this would be possible by avoiding the method of reduction which may cause isomerization of the hydroxyl group which was entered. As proved in the epimerization of borneol by the authors, such reducing agents as copper chromite, sodium or aluminum isopropylate are effective catalysts of epimerization[6]. Therefore, these were not used for the present purpose. Reduction with lithium aluminum hydride and Raney nickel were the methods mostly utilized for this purpose.

When camphorquinone absorbs 1 molar hydrogen, it leads to hydroxy-ketone and giving a diol on further reduction. As an analogous mode of reduction of camphor, Raney nickel or lithium aluminum hydride should give *exo-* and *endo-* isomer with a preponderance of the former. Hydroxy-ketone obtained by these methods can now be assumed to be isomeric with "α-hydroxycamphor" (V) and "β-hydroxycamphor" (VI) by zinc- acetic acid reduction. $LiAlH_4$ reduction of camphorquinone is expected to yield one *cis-* and two *trans-*isomers. On the other hand, however, further reduction of V or VI, separated from each other, should lead to one *cis-*, one *trans-*, respectively. A *cis*-diol can thus be easily purified in $LiAlH_4$ reduction, but it must be somewhat hard in the case of *trans*-diol to purify one from another.

cis-Diol I.—Camphorquinone in ether was reduced with lithium aluminum hydride after Trevoy and Brown's method[7] at dry-ice temperature. Crude *cis*-diol was converted to acetonide, rectified over a sodium ribbon till no more O–H absorption is detected in the 3500 cm^{-1} region of infrared spectra**. After regeneration of the diol, it was recrystallized from ligroin and repeatedly sublimed in vacuo.

cis-Diol II.—"β-Hydroxycamphor" VI purified through its dimolecular methyl ether[8] was hydrogenated over Raney nickel at room temperature, a *cis*-diol was separated from one *trans*-isomer and purified similarly as in the case of I.

trans-Diol III.—The *trans*-diol separated from II in the foregoing reduction product was repeatedly treated with acetone to remove any trace of remaining *cis*-diol.

trans-Diol IV.—The *trans*-diol isolated from Raney nickelhydrogenated diols of "α-hydroxycamphor" V was further purified like III.

Assignment of Conformation.—Tentative assignment of *cis*-I, II and *trans*-III, IV were separately performed by comparison with I.R. spectra at O–H region.

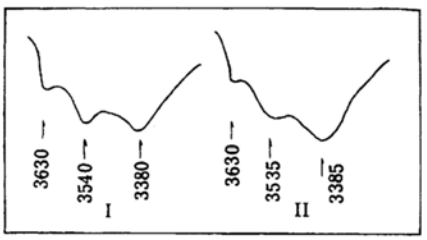


Fig. 2. O–H stretching region (*cis*-diols) CS_2 soln.

The bands at 3540 are intra-molecular O–H; and difference from free O–H, $\Delta\nu=90$, in case of I and 195 in case of II, corresponds to 1.5Å for O–H distance. Concerning the inter-molecular band, intensity of associated O–H/free O–H is a measure of the ease with which solute associates. Thus, as proved in case of borneol[5], the degree of association is far less in *exo-* than that in *endo-*, owing to *gem-* dimethyl hindrance. Of the two *cis*-diols investigated, I can not associate so much as II since the ratio obtained is 291.0 and 416.0%, respectively. Therefore, so far as two *cis-*epimers are concerned, I can be assigned as *exo-*, and II, in turn, as *endo-*. These assigned stuctures of I and II are satisfied with some difference of chemical property,

TABLE II. SAPONIFICATION OF *cis*-DIOL DIACETATES

Isomer	0.1 N KOH, hr.	% Sap'd	25±1°C
I	3	62.9	
II	3	69.1	

7) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949).
** No isomerization of acetonide occurs by distillation over sodium (by I. R.).
8) J. Bredt, *J. prakt. Chem.*, **121**, 153 (1929).

TABLE III. INFRARED SPECTRA OF *trans*-DIOLS

	Free	Int.	Inter	Int.	Ratio	Concn.	Assignment
III	3625	0.232	3450	0.064	27.6%	100.0 mg./10 ml.	*endo-exo-*
IV	3620	0.234	3440	0.057	24.4	〃	*exo-endo-*
III	3620	0.280	3440	0.099	35.4	120.0	*endo-exo-*
IV	3620	0.282	3440	0.085	30.1	〃	*exo-endo-*

Cell length 0.5 mm.

that is, the difference of saponification velocity of corresponding diacetate, as shown in Table II.

The slower saponification rate of I coincides well with the assignment by I. R. And as will be reported in a later paper[9], epimerization of I resulted in a great preponderance of II over I. This corresponds with the known stability of *endo*-isomer in case of borneol.

trans-Diols, III and IV, were similarly compared on the infrared spectra. Although associated OH can best be compared in CCl_4 or CS_2 because a solvent molecule such as $CHCl_3$ is known to prevent intermolecular association of solute***, spectra were taken in $CHCl_3$ solution on account of sparing solubility of *trans*-diol in CS_2****. Therefore, the difference of ratio of polymeric OH/free OH between III and IV was not one-sided as in the case of *cis*-diols. Table III shows comparison of spectra.

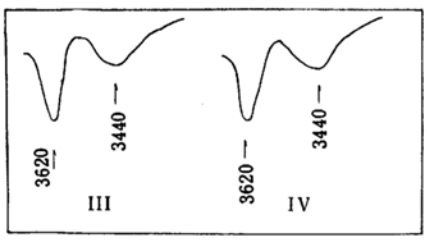


Fig. 3. O-H stretching region (*trans*-diols) $CHCl_3$ soln.

Steric hindrance of *gem*-dimethyl is usually more profound at C_2 than at C_3 because of proximity of adjacent quaternary methyl. That the steric effect of *gem*-dimethyl observed for C_3-OH is not significant has been reported on epi-borneol by Lipp et al.[10] Therefore, an isomer with more bonded OH is suggested to be *2-endo-3-exo-*. This tentative assignment is also supported by the fact that the di-acetate of III is saponified faster than that of IV, as shown in Table IV.

TABLE IV. SAPONIFICATION OF *trans*-DIOL DIACETATES (25±1°C)

Isomer	0.1 N KOH hr.	% Sap'd
III	2	73.1
IV	2	61.3

The properties of four diasteroisomeric diols isolated are summarized in Table V.

TABLE V. PROPERTIES OF DIOLS

Isomer	m. p.(°C)	$[\alpha]_D$	O-H dist.	Conformation
I	262~263	−19.3	1.5 Å	*2-exo-3-exo-*
II	224~225	+30.8	1.5	*2-endo-3-endo-*
III	253~254	+15.0	(3.3)	*2-endo-3-exo-*
IV	251~252	+ 7.7	(3.3)	*2-exo-3-endo-*

Isomeric Composion of Diols by Various Methods of Syntheses.—Diols prepared by direct reduction of camphorquinone and by further reduction of hydroxyketone obtained by zinc-acetic acid reduction of camphorquinone were studied then by infrared spectra. The result of one-step hydrogenation is given in Table VI.

Catalytic hydrogenation affords mainly *cis*-I with some II, *trans*-diols increase with rise of reaction temperature. Therefore, reduction at room temperature easily gives *cis*-diols (I+II) in over 90% yield, though *cis*-I is not easy to purify.

$LiAlH_4$ reduction was much influenced by temperature on the reaction product, *cis*-diol obtained at −70°C being exclusively *exo-*, while that of 0°C was contaminated with *endo-*. Thus, the reduction at dry ice temperature is the procedure employed in this paper for the preparation of uncontaminated *cis-exo*-diol. The Meerwein-Pondorff-Verley type reduction of camphorquinone yielded a characteristic product that consisted of *cis*-diols solely, with very few *trans* isomers. And moreover, II increased considerably, compared with other procedures.

Diols Prepared by Hydrogenation of Hydroxy - camphor. — Camphorquinone

9) T. Takeshita, Presented at the Symposium on Terpenes, held at Hiroshima University, Oct. 10, 1958.

*** The association of ROH in $CHCl_3$ is known to be less than in CS_2. The effect of $CHCl_3$ must be the hydrogen bonding power of CH besides the polarity or molecular size of solvent. (Cf. L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules", Methuen and Co, London (1958), p. 100.

**** Limited solubilty of III in $CHCl_3$, less than 130.0 mg./10 ml., makes possible only narrow concentration range for the present purpose, though IV is more soluble.

10) P. Lipp et al., *Ber.*, **68**, 249 (1935).

TABLE VI. REDUCTION PRODUCT OF CAMPHORQUINONE

Expt.	Reducing agent	I	II	III	IV	Remarks	
1	Raney Ni	88	5	1	6	14～20°C	8 hr.
2	〃	75	7	1	17	90～100	9
3	Copper chromite	54	6	9	31	120～150	3
4	Al-(O-*i*Pr)$_3$	60	39	—	1	88	10
5	$LiAlH_4$	89	4	4	3	0	20
6	〃	94	—	3	3	−70	20

TABLE VII. REDUCTION PRODUCT OF HYDROXYCAMPHOR

Expt.	Starting epimer	Reducing agent	I	II	III	IV	Remarks	
7	β-	Raney nickel	—	48	52	—	20～27°C	10 hr.
8	β-	〃	—	41	59	—	29～34	8
9	α-	〃	14	41	—	45	17～18	12
10	α-	〃	12	34	—	54	32～40	6
11	β-	$LiAlH_4$	—	85	15	—	0	20
12	α-	〃	19	69	—	12	0	20
13	β-	Na-EtOH	—	19	16	65	80～90	5
14	α-	〃	—	22	12	66	80～90	5

yields hydroxy-ketone on zinc-acetic acid reduction, which has been reported to consist of α-hydroxycamphor and β-hydroxycamphor[11]. The configuration of this hydroxycamphor is not clear, but must be *endo*-configuration since β-isomer which was regenerated from sparingly soluble dimolecular methyl ether afforded *cis-endo*-diol. The result of reduction of this hydroxyketone also supports this idea as indicated in Table V.

A point to be noticed is that *cis*-diol obtained from β-hydroxycamphor catalytically or with $LiAlH_4$ was *cis-endo*, while that from α-isomer afforded *endo*- mixed with about one third the amount of *exo*-isomer. This shows the homogenity of β-isomer, *endo*- whereas α-isomer was a mixture of *endo*- and *exo*-, in ratio of 3 to 1. The catalytic hydrogenation of hydroxycamphor presents an interesting problem, since predominant *exo*-addition observed in case of camphor[4] was cut to about half to give *trans*-diol. This indicates steric hindrance in opposing direction by *gem*-dimethyl group to that of *endo*-hydroxyl group. Thus, $LiAlH_4$ reduction gives only 15% of *exo*-reduced product because lithium aluminum salt formed with *endo*-hydroxyl group becomes overwhelmingly bulkier than the *gem*-dimethyl, *exo*-directing radical. Sodium with alcohol gave mostly *trans*-diol as the usual mode of *trans*-addition. Similarity of the reduction product is considered to be isomerization of β-hydroxycamphor to α-isomer as seen in Experiments 13 and 14.

11) β-Hydroxycamphor, so designated, is actually α-hydroxy-epicamphor.

Experimental[12]

I. *exo-exo*-2, 3-Camphane-diol.—A solution of camphorquinone (10 g.) in ether was added dropwise at −60°C to −70°C to an ether solution of $LiAlH_4$ (c=1.6 mol./l.) immersed in a methanol-dry ice bath and kept for 20 hr.[6] After decomposition of excess of reagent with water, the whole was washed with dilute sulfuric acid, saturated sodium chloride solution, dried with anhydrous sodium sulfate and the solvent was evaporated to give the *cis*-diol (9.5 g.). Seven grams of crude product was treated with acetone by the procedure of Rupe et al.[2] to give acetonide (8.4 g.), and vacuum distillation afforded some *trans*-isomer (0.43 g.). Acetonide was purified by rectifying over sodium till it showed no more hydroxyl absorption in 3500 region of its infrared spectra, 4 g. of pure acetonide was saponified to regenerate *cis*-diol (2.7 g.), recrystallized from ligroine, and sublimed in vacuo, m. p. 262～263°C, $[\alpha]_D$−19.3 (c=0.50000 g./5 ml.).

II. *endo-endo*-2, 3-Camphane-diol. — "β-Hydroxy-camphor" (27.7 g., m. p. 204～205°C), purified through dimolecular methyl ether (m. p. 147～148°C)[8,13] was hydrogenated in alcohol over Raney nickel at 14～20°C to yield *cis*-diol (28.0 g.) mixed with *trans*-isomer. To isolate *cis*-diol, 20 g. of diol was treated as I with acetone. The solid product (21.0 g.), wet with *cis-endo*-acetonide was extracted with boiling hexane to free it from *trans*-diol. Evaporation of hexane afforded acetonide contaminated with some *trans*-isomer; this was further treated over sodium as I, saponified, recrystallized, and vacuum sublimed.

12) All melting points are uncorrected. All rotations were measured in 1 dm. tube as an alcoholic solution. Infrared spectra were taken with a Perkin Elmer Model 21 Infrared Spectrophotometer equipped with sodium chloride prism.

13) J. L. Simonsen mis-stated the m. p. of the compoud as 37～38°C in "Therpenes", Vol. II, Cambridge University Press, Cambrige (1949), p. 428.

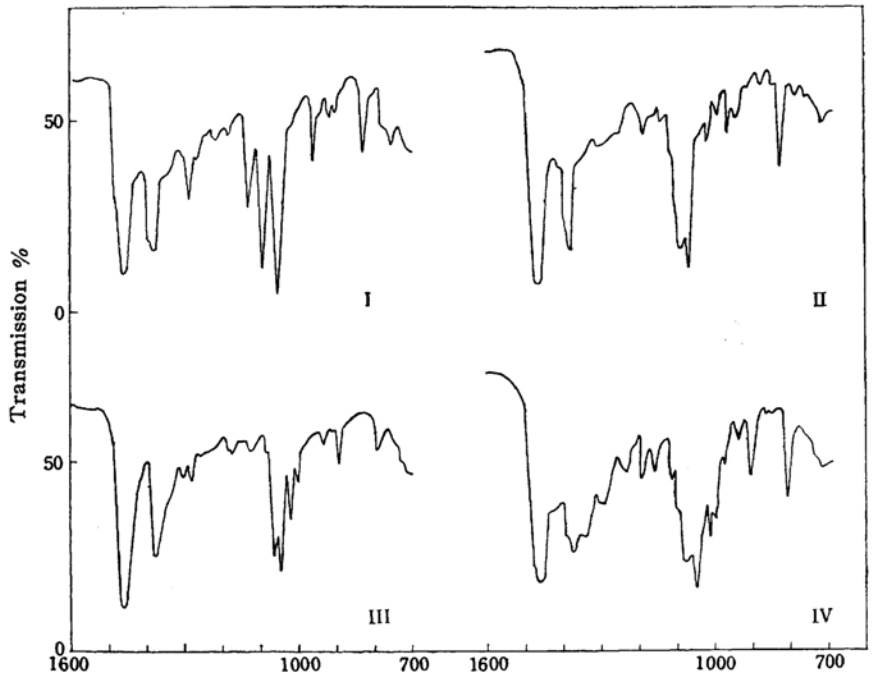


Fig. 4. I. R. of diols (as Nujol mulls)

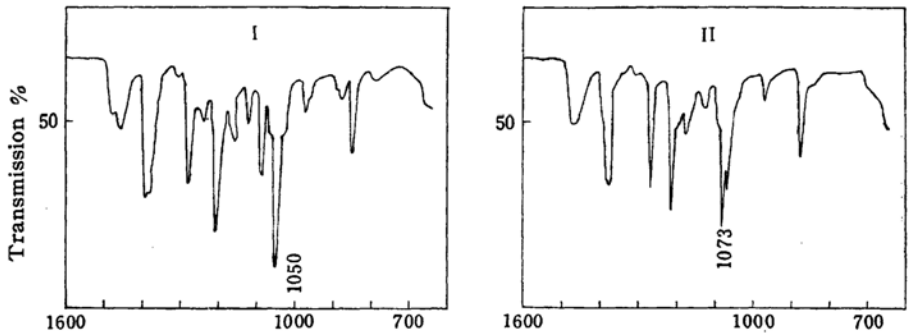


Fig. 5. I. R. of *cis*-acetonide (1600～1650 cm^{-1}) cap.

Yield, 3.6 g., m. p. 224～225°C, $[\alpha]_D$ +30.8 (c= 0.50000 g./5 ml.).

III. *endo-exo*-2,3-Camphane-diol. — The *trans*-diol separated (9.2 g.) in isolation of II was further treated with acetone to remove any trace of *cis*-diol present and recrystallized several times from ligroine and sublimed in vacuo. Yield, 7.5 g., m. p. 253～254°C, $[\alpha]_D$+15.0 (c=0.50000 g. /5 ml.).

IV. *exo-endo*-2,3-Camphane-diol.—Similarly as in the case of III, *trans*-isomer separated from hydrogenation of 8.5 g. of "α-hydroxycamphor" was further treated with acetone, to remove *cis*-isomer, recrystallized sublimed in vacuo, m. p. 251～252°C, $[\alpha]_D$ +7.7 (c=0.50000 g./5 ml.).

Infrared Measurement — All the spectra were taken by Perkin Elmer Model 21 with NaCl Optics. The infrared determination of the isomeric composition of diols which resulted as reduction product was developed as follows.

As stereoisomeric cyclic alcohol usually has a characteristic band around the 1000～1100 region like those of *endo*- and *exo*- borneols[5], the spectra of four isomers are distinguishable (Fig. 4) in this region. These are, however, only effective for qualitative analysis because of the overlapping of bands not at the peaks but at the side of absorption maxima. As shown in the preceding discussion, in dilute solution, *cis*-diols absorb both at 3620 and 3520, while *trans*-isomer does so at only 3620 owing to absence of intra-molecular band of 3520. Thus, *cis-trans* composition can be determined by O—H stretching bands. Individual epimers are then determined by C—O stretching region.

1) Intensity of 3620 and 3520 bands measured.

Diols		3620	Average	3520	Average
cis-	I	0.223	0.217	0.166	0.166
	II	0.211		0.165	
trans-	III	0.351	0.354	0.048	0.046
	IV	0.356		0.044	

Concn. 60.0 mg./10 ml. $CHCl_3$
Cell length 1.2 mm. Room temp. 25±2°C

At the concentration indicated, there was not much variation in optical density between isomers within the same geometrical group (*cis*- or *trans*-), and this presents a rapid method of determination of *cis*- and *trans*-isomers. Trial analysis of some synthetic mixtures of known concentration was found to be accomplished with 2% error, this accuracy being sufficient for the present study.

	cis		*trans*		*cis*		*trans*	
Synthetic	II	66.5	IV	33.5	II	33.2	III	66.8
Found		67.2		32.8		34.9		65.1
Synthetic	I	83.2	IV	16.8	III	83.2	III	16.8
Found		85.0		15.0		85.8		14.2

On finding *cis-trans* ratio, determination of each isomer is performed by C—O stretching region.

2) Intensity of C—O stretching region.

Diols	1089	1074	1060
I	0.312	0.095	—
II	0.203	0.282	0.368
III	0.068	0.271	0.168
IV	0.067	0.098	0.401

Concn. 60.0 mg./10 ml. $CHCl_3$
Cell length 0.5 mm.

Fortunately, the 1089 intensity of III and IV does not differ much. *Trans*-contribution at this wave number can be treated as equal in evaluation of *trans* isomers of diols. Compositions III and IV are finally determined after *cis*-diols were removed with acetone as acetonide. Trial analysis was performed with 2% error as follows:

Synthetic	II	66.5	IV	33.5	II	33.2	III	66.8
Found		65.0		35.0		31.0		69.0
Synthetic	I	83.2	IV	16.8	IV	66.5	III	33.5
Found		84.9		15.1		68.3		31.7
Synthetic	III	35.0	IV	65.0				
Found		36.6		64.3				

Thus the ratio of epimers was found to be analyzed on a 2-component system using C—O stretching region with 2% error. However, overall error of analysis amounts to less than 4%, with assay of *cis-trans* ratio combined in analysis of diols. As to *cis*-isomers I and II, characteristic *cis*-acetonide was compared with them. (Fig. 5)

Saponification of Diol Diacetate.—Acetylation of diol was as follows: Each of the diols (3 mmol., 510 mg.) was gently boiled with acetic anhydride (Purity 94.2%, 2.1 g.) and anhydrous sodium acetate (0.4 g.) for 1 hr., settled overnight, the excess of reagent decomposed with 10 ml. of hot water during 2 hr., extracted with ether. After being washed with aqueous solution of sodium chloride, and then sodium bicarbonate, the solution was dried over anhydrous sodium sulfate. Removal of solvent in vacuo, finally by warming at 110°C/7 mmHg afforded slightly colored diacetate oil, in yield ranging from 600 to 700 mg. Purity found. (Theor. Value, Ester Value 441.0 as $(CH_3COO)_2 \cdot C_{10}H_{16}$) Diacetate of I E. V. 427.3, II E. V. 434.5, III E. V. 435.1, IV E. V. 428.1

The diacetate thus prepared was saponified by the usual procedure: Weighed sample, equivalent to 10 ml. of 0.1 N alcoholic KOH, in bottle was immersed in a water bath kept at 25±1°C. To this was added 10 ml. of 0.1 N alcoholic KOH at 25±1°C and maintained at this temperature. Back titration with 0.1 N H_2SO_4 against phenolphthalein gave the amount saponified. (Cf. Table II and IV).

Preparation of Diols by Various Methods.

Expt.	Camphorquinone (g.)	Catalyst		Solvent (ml.)		Temp. (°C)	Time (hr.)	Yield (g.)	m.p. (°C)	$[\alpha]_D$
1	25	Raney Ni	6 g.	EtOH	30	14～20	8	25	253～255	−13.9
2	33.2	〃	6 g.	〃	30	90～100	9	33.3	250～252	− 9.6
3	8.3	Copper chromite	3 g.	Benzene	10	120～150	3	7.8	245～249	− 4.6
4	8.3	Aluminum isopropylate	20 g.	IsoprOH	200	85～88		4.7	241～242	+ 1.9
5	6.6	$LiAlH_4$	0.04mol.	Ether	30	0	20	6.2	256～257	−16.5
6	10.0	〃	0.06mol.	〃	200	−70	〃	9.5	255～257	−15.7
7	β- 27.7	Raney Ni	6 g.	EtOH	20	20～27	10	25.3	232～234	+20.0
8	β- 7	〃	3 g.	〃	15	29～34	8	6.2	232～235	+22.6
9	α- 8.5	〃	3 g.	〃	15	17～18	12	8.2	235～238	+11.2
10	α- 7	〃	3 g.	〃	15	32～40	6	6.8	238～241	+ 8.3
11	α- 4.2	$LiAlH_4$	0.013mol.	Ether	20	0	20	4.0	226～228	+28.7
12	β- 4.2	〃	〃	〃	〃	〃	〃	3.6	229～231	+15.6
13	β- 6.7	Na	9.2 g.	EtOH	150	80～90	5	4.8	229～231	—
14	α- 4.0	〃	6 g.	〃	90	〃	〃	3.2	233～234	+11.9

Expts. 1—3) *Reduction of camphorquinone.*—Camphorquinone was hydrogenated in 100 ml. stainless steel autoclave equipped with magnetic stirring-valve. Initial press., 70～120 kg./cm².

Expt. 4) The Meerwein-Pondorff-Verley reduction of camphorquinone was carried out by the usual method, maintaining the inner temperature below 89°C.

Expts. 5 and 6) Lithium aluminum reduction followed after the procedure of Trevoy and Brown[6]. $LiAlH_4$, ether solution (1.6 M).

Expts. 7—10) *Reduction of hydroxycamphor.*—The hydroxycamphor used in the experiment was synthesized after Bredt's method[8]. Catalytic hydrogenation of α- and β-hydroxycamphor were carried out, using Raney nickel.

Expts. 11 and 12) Lithium aluminum hydride reduction is analogous to that of the foregoing.

Expts. 13 and 14) Reduction of hydroxycamphor with sodium in alcohol was by the usual procedure.

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