

556. Reductions with Aluminium Alkoxides. Part I. The Relative Proportion of Epimers in Alcohols derived from Cyclic Ketones.

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Reductions of seven cyclic ketones were carried out with aluminium isopropoxide, and the composition of the mixtures of epimeric alcohols was determined in each case. The proportion of *cis*-epimer was greatest from those ketones in which steric hindrance was greatest. This would be expected if the reduction proceeded through a cyclic transition state. The proportion of epimers was independent of the method of carrying out the reduction.

Reductions of menthone with the aluminium derivatives of four secondary alcohols showed that increasing the steric hindrance in the reducing alcohol increased the proportion of *cis*-epimer.

WHEN a ketone is reduced by the Meerwein-Ponndorf method the possibility often arises of getting a mixture of epimeric alcohols. This will always be the case for an open-chain ketone already containing a centre of asymmetry, and usually the case for a cyclic ketone with substituents in the ring. A recent review (Wilds, "Organic Reactions", Vol. II, Wiley and Sons, 1944) shows that no systematic work has been done which might enable one to predict the relative proportions of epimers in any particular case. In the present research some information has been obtained on the proportions of epimers from substituted *cyclohexanones*, and this allows a certain amount of generalisation.

The work is divided into two parts. In the first part details are presented of the reduction of some substituted *cyclohexanones* with aluminium isopropoxide in isopropyl alcohol, and the calculation of the amounts of *cis*-epimer in the mixtures of alcohols produced.

Reduction of ketones with aluminium isopropoxide.

Ketone.	<i>cis</i> -Alcohol in mixture.	Property used to assay mixture.
(±)-2-Methyl <i>cyclohexanone</i>	50%	Density, d_4^{20} 0.9222
(±)-3-Methyl <i>cyclohexanone</i>	55	" 0.9106
4-Methyl <i>cyclohexanone</i>	33	" 0.9084
4- <i>iso</i> Propyl <i>cyclohexanone</i>	40	" 0.9092
(-)-4- <i>iso</i> Propyl <i>cyclohex-2-en-1-one</i>	39	Rotation, α_D^{17} -47.4°
(-)-Menthone	70	Rotation, α_D^{20} +0.8°
(+)-Camphor	70	Rotation of <i>p</i> -nitrobenzoates

The results are summarised in the table, and it is seen that as the apparent degree of steric hindrance of the carbonyl group increases, owing to the proximity of bulky alkyl groups, the yield of *cis*-epimer also increases. When alkyl groups are in position 4 relative to the carbonyl group the yields of *cis*-epimer are least, and there is a marked increase in *cis*-content when there is a substituent in position 2, particularly when this substituent is large, as in menthone and camphor.

The factor chiefly determining the relative amounts of *cis*- and *trans*-epimers is believed to be steric hindrance of the carbonyl group, but the relative stabilities of the epimers may also be important in some cases. None of the epimers from the ketones studied was markedly unstable, and in the absence of marked differences in stability it seems probable that some of each epimer will be formed in all cases.

The ketones studied were chosen because of their accessibility, and the fact that there was available enough information on the corresponding epimeric alcohols to enable the mixtures to be analysed readily. The preparations of 4-*isopropylcyclohexanone* and *cis*- and *trans*-4-*isopropylcyclohexanol* were effected by methods different from those previously used, and slightly different physical constants were observed. The method of separating epimeric mixtures by partial esterification (cf. this vol., p. 1717) was applied to the 4-*isopropylcyclohexanols* and the borneols; for the former, *o*-phthalimidobenzoyl chloride was a suitable reagent, and for the latter *o*-nitrobenzoyl chloride gave a very easy separation.

Some experimental results published by other workers show in a general way the same trend as in the above table. For the reduction of steroids with a carbonyl group at position 3, which is relatively unhindered, information available seems to indicate that alcohols of *cis*- and *trans*-configuration are formed in approximately equal amounts, particularly in the reduction of cholest-4-en-3-one (Schoenheimer and Evans, *J. Biol. Chem.*, 1936, **114**, 567), cholesta-4 : 7-dien-3-one (Windaus and Kaufman, *Annalen*, 1939, **542**, 218), and ergosta-4 : 7 : 17-trien-3-one (Windaus and Bucholz, *Ber.*, 1938, **71**, 576; 1939, **72**, 597).

The case of androsta-3 : 5-dien-17-one (Butenandt, Heusner, von Dresler, and Meinerts,

Ber., 1938, **71**, 198), an example of reduction at position 17 which is relatively hindered and part of a five-membered ring, shows a preponderance of *cis*-epimer, judging from the amount of each epimer isolated. Examples from the chemistry of steroids are quite numerous, but many are of dubious value, because of the complex nature of the molecule, the difficulties of analysis, and the poor overall yields.

Published examples in terpene chemistry are relatively few, and yields are often unsatisfactory. Dihydrocarveol is reported (Johnston and Read, *J.*, 1934, 233) to give a good yield of dihydrocarveol, of which 60% is *cis*-epimer, as would be expected for a substance similar in structure to menthone but rather less hindered. Carvone (Johnston and Read, *loc. cit.*) and menth-4-en-3-one (Malcolm and Read, *J.*, 1939, 1037) appear to give about 50% of *cis*-alcohol in each case and, although they are of a type not represented in the present research, the directive influence operating should not be substantially greater than that in 3-methylcyclohexanone, as the alkyl group adjacent to the carbonyl group is coplanar with the cyclohexane ring, and, although it may hinder strongly, cannot effectively direct the preferential formation of *cis*- or *trans*-epimer. Figures for menthone (Read and Grubb, *J. Soc. Chem. Ind.*, 1934, **53**, 52r; Zeitschel and Schmidt, *Ber.*, 1926, **59**, 2303) and 4-isopropylcyclohex-2-en-1-one (Gillespie, Macbeth, and Mills, *J.*, 1948, 996) are now confirmed.

Two papers have been published differing from the present results. In the reduction of 2-methylcyclohexanone by aluminium isopropoxide, Anziani and Cornubert (*Bull. Soc. chim.*, 1945, **12**, 359) reported a 90% yield of *trans*-alcohol, basing this on the melting point of the derived phenylurethane. Mousseron, Marszak, and Bolle (*Bull. Soc. chim.*, 1943, **9**, 260) stated that (+)-3-methylcyclohexanone gave 30% of (-)-*cis*-3-methylcyclohexanol, but a preliminary fractional distillation was carried out before this figure was calculated from the rotations of the fractions. We believe that direct assay of the reaction mixture, without any preliminary separation, is more reliable.

Marvel and Moore (*J. Amer. Chem. Soc.*, 1949, **71**, 28) have presented data which show that the reduction of ethyl 1-cyano-4-keto-2 : 6-diphenylcyclohexane-1-carboxylate with aluminium isopropoxide yields a slight excess of the *trans*-epimer, as would be expected, but neither epimer was isolated as such, the *cis*-epimer being converted into a lactone and the *trans* into a linear polymer.

Although evidence is at present too meagre for any useful comparison to be made between results for aliphatic and alicyclic ketones, it may be noted that benzoin is reported to give 90% of *meso*hydrobenzoin on reduction by aluminium isopropoxide (Lund, *Ber.*, 1937, **70**, 1520), and that Lutz and his co-workers (*J. Amer. Chem. Soc.*, 1948, **70**, 2015; 1949, **71**, 478) have observed a preponderance of one epimer in the mixture from the reduction of derivatives of α -aminodeoxybenzoin.

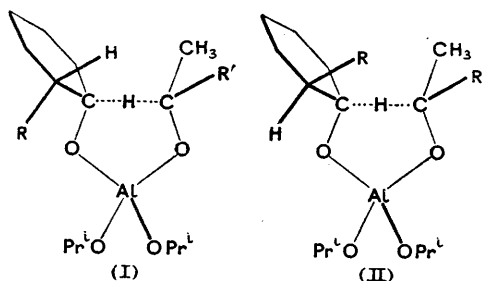
The influence of steric hindrance on the proportion of epimers is also seen in the second part of this research, in which the relatively hindered ketone menthone was in turn reduced with the aluminium derivatives of methylethylcarbinol, methylisobutylcarbinol, and methyl-*tert.*-butylcarbinol, under conditions the same as for aluminium isopropoxide. The amount of *neomenthol* (*cis*-epimer) in the product was higher in each case than the 70% observed for aluminium isopropoxide and, although the actual figures obtained (75%, 72%, and 86%, respectively) may not be completely accurate, there was a definite trend to increased *cis*-content as the steric hindrance in the reducing alcohol was increased.

(-)-Menthone was chosen because of its relatively hindered nature, the impossibility of racemisation, and the ease of assay of the products by measurement of optical activity. It had the disadvantage of undergoing partial inversion to (+)-*isomenthone* before reduction (this was also found when it was heated with a solution of aluminium *tert.*-butoxide), and the mixture of (-)-menthol and (+)-*neomenthol* was contaminated with (+)-*isomenthol* and (+)-*neoisomenthol*. An estimate of the amount of (+)-*neomenthol* actually formed from (-)-menthone was still possible on making two assumptions: that (+)-*isomenthone* gives rise to the same proportion of *cis*-alcohol as does (-)-menthone, and that the rotation of any one of the menthols in a mixture is independent of the presence of the others. The second assumption has not been proved for complex mixtures of the type encountered, but it is probably valid, as Read has shown (*Chem. Reviews*, 1930, **7**, 1; *J.*, 1934, 313) that in alcohol the menthols obey the rule of optical superposition. The extent of inversion to (+)-*isomenthone* was found by oxidising the menthol mixture back to menthone and determining the amount of (+)-*isomenthone* in the product. Reductions with aluminium isopropoxide and *sec.*-butoxide caused only small inversions, and errors from this in the calculated proportions of *cis*-epimer are certainly very small, but with the other alkoxides considerable inversion was found and

accurate analysis of the mixtures was more difficult. However, it is believed that the trend in proportion of *cis*-epimer is real, notwithstanding the anomalous result with methylisobutylcarbinol.

All experiments except that with methyl-*tert.*-butylcarbinol were done in duplicate, and the two sets of results were indistinguishable. Very good yields of alcohols were always obtained. The reductions were done by the conventional procedure for the Meerwein-Ponndorf reduction, rather than by the modified procedure in which the concentration of ketone is kept low (see following paper), but it was shown for (–)-menthone and (–)-4-isopropylcyclohex-2-en-1-one that the same proportion of epimers was obtained by the modified procedure. (–)-Menthone gave the same proportion of epimers whether the reduction was done with 0.5, 1.0, or 3.0 equivalents of aluminium isopropoxide per mole of menthone. Aluminium isopropoxide caused about the same degree of inversion of (–)-menthone whether the reduction was done by the conventional procedure or the modified procedure.

The results of the present research have been considered in conjunction with the theory of a cyclic transition state in the Meerwein-Ponndorf reduction. Two possible configurations for the transition state in the reduction of a 2-alkylcyclohexanone are shown below, (I) leading to the formation of *cis*-2-alkylcyclohexanol and (II) to the *trans*-epimer. Construction of models



suggests that if the group R is large, the configuration (I) should be favoured, because there is more possibility of steric hindrance in (II), and that if the group R' in the reducing alcohol is also large it increases the steric hindrance associated with (II). Although the present work cannot be shown to prove or disprove the theory of a cyclic transition state, it does offer a limited support for it.

The results obtained have some practical significance. When the Meerwein-Ponndorf reduction is applied to a cyclic ketone which may give rise to epimeric alcohols, a mixture of these must always be expected, often with comparable amounts of the epimers. If their separation is likely to be difficult, other, more selective, methods of reduction may be better for the preparation of individual epimers. In cases where the Meerwein-Ponndorf method has to be used, it may be possible to effect a separation of the epimers by applying the method of partial esterification, as exemplified by this paper, a previous paper (this vol., p. 1717), and papers by Read and his co-workers (*J. Soc. Chem. Ind.*, 1934, 53, 52r; *J.*, 1934, 233, 1779). This method may not be successful with 3-alkylcyclohexanols.

EXPERIMENTAL.

Sources of Ketones and Reference Alcohols.

Ketones.—(±)-3-Methylcyclohexanone was obtained by oxidising pure (±)-*trans*-3-methylcyclohexanol (from the hydrogen phthalate) as described by Macbeth and Mills (*J.*, 1945, 709).

(±)-2-Methylcyclohexanone, d_4^{20} 0.9160, and 4-methylcyclohexanone, d_4^{20} 0.9072, were obtained from the corresponding cresols, which were recrystallised to constant m. p. from light petroleum and then hydrogenated over Raney nickel at 150–180°; the reduction products were freed from traces of cresol and oxidised by the method used for 3-methylcyclohexanol.

(–)-4-*iso*Propylcyclohex-2-en-1-one was isolated from the oil of *Eucalyptus cneorifolia*, and had α_D^{19} –64.7° (Berry, Macbeth, and Swanson, *J.*, 1937, 987).

Hydrogenation of this unsaturated ketone over Raney nickel at 140°, followed by oxidation of the 4-*iso*propylcyclohexanols with dichromate, gave impure 4-*iso*propylcyclohexanone. The impure ketone (79 g.) was warmed with benzhydrazide (76.5 g.) in alcohol (100 ml.) containing acetic acid and sodium acetate (2 g. each), and from the reaction a product was isolated (133 g.) with m. p. 125–133°. Two recrystallisations from toluene–light petroleum (1:1) gave the pure *benzoylhydrazone* (114 g.) as fine white needles, m. p. 133–134° (Found: N, 10.8. $C_{16}H_{22}ON_2$ requires N, 10.85%). The pure hydrazone (20 g.) was hydrolysed by heating it under reflux for 1 hour with sulphuric acid (20 g.) in 50% alcohol (120 ml.), and from the mixture was recovered 4-*iso*propylcyclohexanone in 90% yield,

with d_4^{20} 0.9099 and n_D^{20} 1.4567. It was essential to wash the liberated ketone with dilute alkali to remove benzoic acid.

(-)-Menthone was made in 92% yield by the oxidation of (-)-menthol with dichromate, following the method in *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 340, but with better precautions against inversion during working up. The menthone was dissolved in ether, washed with ice-cold alkali, and distilled under reduced pressure; it had α_D^{25} -24.8° (homogeneous).

(+)-Camphor was taken from a batch known to be satisfactory for cryoscopic work.

Methylcyclohexanols.—Published physical constants for pure epimeric 3-methylcyclohexanols (Macbeth and Mills, *loc. cit.*) and 2- and 4-methylcyclohexanols (Jackman, Macbeth and Mills, *loc. cit.*), were used.

4-isopropylcyclohexanols.—The mixture, d_4^{20} 0.9092 (46 g.), of *cis*- and *trans*-4-isopropylcyclohexanols resulting from the Poindorf reduction of 4-isopropylcyclohexanone was mixed with pyridine (150 ml.) and subjected to competitive esterification with *o*-phthalimidobenzoyl chloride (Gabriel and Löwenberg, *Ber.*, 1918, **51**, 1495) (68 g., 0.7 mol.) in warm chloroform (150 ml.). In working up the product it was not possible to steam-distil the unesterified alcohols directly out of the ester, as the latter was solid at 100° ; therefore the ester was precipitated from solution as completely as possible with light petroleum, and the mother liquor was steam-distilled. Ester (84 g., 90%), m. p. $148-150^\circ$, and unesterified alcohol (11.6 g., 84%), d_4^{20} 0.9114 (87% *cis*-), were recovered.

The crude ester was recrystallised from a mixture of toluene and light petroleum (1 : 1), and pure *trans*-4-isopropylcyclohexyl *o*-phthalimidobenzoate was obtained as large needles, m. p. $151.5-152.5^\circ$ (75%); (Found: N, 3.7. $C_{24}H_{25}O_4N$ requires N, 3.6%). The pure ester was hydrolysed by heating it under reflux for 2 hours with a 5% solution of potassium hydroxide (2.2 moles) in methanol. Hydrolysis with 1 mole of potassium hydroxide was incomplete, apparently because of simultaneous opening of the phthalimide ring. The *trans*-4-isopropylcyclohexanol recovered (84%) had b. p. $94/5$ mm., d_4^{20} 0.9073, n_D^{20} 1.4662.

The unesterified 4-isopropylcyclohexanol (87% *cis*-) was completely esterified with *p*-nitrobenzoyl chloride, giving an ester, m. p. $45-51^\circ$. This ester reached purity after 3 recrystallisations from light petroleum and 2 from isopropyl alcohol. The pure ester was dimorphic; crystallisation from isopropyl alcohol usually gave fine needles, m. p. $69.5-70.5^\circ$, whereas crystallisation from light petroleum gave large prisms which melted at 65° , then solidified, and melted again at 69° (69.5° was reported by Cooke, Gillespie, and Macbeth, *J.*, 1939, 518). The *cis*-4-isopropylcyclohexanol obtained from this ester had d_4^{20} 0.9120 and n_D^{20} 1.4671.

Menthols.—The method of Read and Grubb (*loc. cit.*) was used to separate pure (-)-menthol and (+)-neomenthol from the mixture resulting from the reduction of (-)-menthone.

Borneols.—A mixture was available which contained approximately equal amounts of (+)-borneol and (-)-isborneol. This mixture, in pyridine, was allowed to react with half of the theoretical amount of *o*-nitrobenzoyl chloride, and the reaction product, freed of pyridine, was steam-distilled to separate unesterified (-)-isborneol from the (+)-bornyl *o*-nitrobenzoate. This ester, after several recrystallisations from light petroleum, formed large pale yellow prisms, m. p. 109° , $[\alpha]_D^{25} +67^\circ$ (*c*, 2 in toluene) (Found: N, 4.9. $C_{17}H_{21}O_4N$ requires N, 4.6%).

The unesterified alcohol was largely (-)-isborneol, and was then completely esterified with *p*-nitrobenzoyl chloride. Five recrystallisations of the ester from alcohol gave pure (-)-*iso*-bornyl *p*-nitrobenzoate, yellow needles, m. p. 130° , $[\alpha]_D^{15} -48.8^\circ$ (*c*, 2 in toluene).

A sample of pure (+)-borneol, obtained by hydrolysis of the pure *o*-nitrobenzoate, was converted into pure (+)-bornyl *p*-nitrobenzoate, m. p. 137° , $[\alpha]_D^{14} +34.9^\circ$ (*c*, 2.5 in toluene).

A series of synthetic mixtures was prepared, each mixture containing a fixed amount (0.25 g.) of (+)-bornyl *p*-nitrobenzoate, but a different amount of (-)-isobornyl *p*-nitrobenzoate. These mixtures were dissolved in a fixed amount of toluene (10 ml.) and the rotations of the solutions determined at 14° . A graph was then constructed to show the relation between rotation and percentage of (-)-isobornyl *p*-nitrobenzoate in the mixture. This procedure was necessary because of the marked dependence on concentration of the specific rotation of (+)-bornyl esters (Henderson and Heilbron, *Proc. Chem. Soc.*, 1913, **29**, 281).

Reductions with Aluminium isoPropoxide.

Apparatus.—The reactions were carried out in a flask provided with a dropping funnel, and attached to a 30-in. lagged fractionating column filled with 0.25-in. porcelain beads and surmounted by an efficient still-head of the total-condensation, partial-take-off type. The fractionating efficiency was about 4 theoretical plates; the hold-up was comparatively large. Heating was done by an oil-bath, the level of the bath being below the level of the solution in the flask. Before each experiment the apparatus was cleaned and dried by heating under reflux in it a dilute solution of aluminium isopropoxide.

Methyl- and isoPropyl-cyclohexanone.—In a typical experiment a 0.68M-solution of distilled aluminium isopropoxide (220 ml., 0.45 equiv.) in isopropyl alcohol was boiled under total reflux until the column was heated through, and then (\pm)-2-methylcyclohexanone (50 g., 0.45 mole), dissolved in dry isopropyl alcohol (60 ml.), was added during several minutes at such a rate that refluxing was maintained. When the temperature at the still-head started to fall, the rate of take-off was adjusted to 10–12 drops per minute, and a high reflux ratio was maintained, with the bath at $145-155^\circ$, and the reaction mixture at about 88° . The temperature at the still-head fell to 64° after 20 minutes, then rose slowly, to reach 82° at the end of 3 hours, whereupon the distillate (total, 50 ml.) was free from acetone (test with 2 : 4-dinitrophenylhydrazine). No additional isopropyl alcohol had been added.

Most of the isopropyl alcohol was removed from the solution through the column at 50° under reduced pressure, and the residue was treated with crushed ice and sulphuric acid (74 ml. of 10N.). The aqueous solution was extracted 3 times with ether (total, 400 ml.), and the combined ethereal extracts were washed in succession with sodium hydroxide solution and water and dried ($MgSO_4$). The

ether was stripped off through a 1-ft. bead-packed column, and distillation of the residue was continued through this column under reduced pressure until the temperature at the still-head became constant. This ensured the removal of isopropyl alcohol and any traces of volatile material which might be present, such as methylcyclohexene. Pure ether was then added, and refluxed in the column to recover the material held up in it. The column was then replaced by a Claisen still-head, the ether was distilled off, and the residue was distilled under reduced pressure. It appeared to be entirely methylcyclohexanols, had a sharp b. p. of $50^{\circ}/2.5$ mm. and left no residue. The mixture of epimeric (\pm)-2-methylcyclohexanols was obtained in 95% yield, and had a_D^{20} 0.9222, which was not altered by a further distillation; it indicates the presence of 50% of *cis*-epimer.

The same conditions were used for the reduction of 3-methyl-, 4-methyl-, and 4-isopropyl-cyclohexanone. Density values could always be duplicated to within 1 part in 10,000, and yields were consistently 93–95%, with only traces of fore-run or residue.

Menthone.—When (–)-menthone was reduced by the above method, reduction was complete in 3.5 hours, and a mixture of menthols was obtained in 92% yield, with a_D^{17} $+0.6^{\circ}$ (homogeneous), changing to a_D^{20} $+0.8^{\circ}$ (homogeneous), $[\alpha]_D^{17}$ 0.0° (*c*, 2 in alcohol), after a second distillation. A portion of the menthol mixture was oxidised as described above, giving menthone with a_D^{15} -20.1° (homogeneous), in 85% yield. From the rotation, a_D^{19} -24.8° , of the original menthone, and the known value a_D^{15} $+82^{\circ}$, for (+)-isomenthone, the extent of inversion to isomenthone was calculated to be 4%.

Making the assumptions explained in the introduction, it was calculated that the reduction of (–)-menthone gives rise to 70% of (+)-neomenthol and 30% of (–)-menthol.

When reaction was carried out with only 0.5 equivalent of aluminium isopropoxide per mole of menthone, but the same concentration of menthone, reduction required 3.5 hours and gave a 93% yield of menthols with a_D^{15} $+0.6^{\circ}$ (homogeneous), which on oxidation afforded a menthone with a_D^{15} -20° . These results are the same as those for 1.0 equivalent of isopropoxide.

The use of 3.0 equivalents of alkoxide for each mole of menthone gave a menthol mixture (92% yield) with a_D^{20} $+1.2^{\circ}$, which passed on oxidation to a menthone with a_D^{17} -18.8° . This indicated 5.5% inversion to (+)-isomenthone, but the proportion of (+)-neomenthol was still very close to 70%.

When the modified procedure (see following paper) was used for the reduction, (–)-menthone (20 g.), a_D^{21} -24.0° , was dissolved in isopropyl alcohol (100 ml.) and added dropwise during 4.5 hours to a refluxing 0.7M-solution of aluminium isopropoxide (190 ml.), from which distillate was collected at the same rate. After a further 0.75 hour the test for acetone was negative. The reduction yielded 96% of menthol mixture, a_D^{18} $+0.6^{\circ}$ (homogeneous), which on oxidation gave menthone having a_D^{16} -20.0° , in 95% yield.

A solution of (–)-menthone (11.5 g.) in dry *tert*-butyl alcohol (50 ml.) was treated with aluminium *tert*-butoxide (7.3 g., 1.1 equivs.) and heated under reflux for 4 hours. During working up on the same lines as for reductions, precautions were taken against further inversion. Menthone was recovered in 91% yield with a_D^{15} -6.8° instead of the original a_D^{15} -24.8° , indicating nearly 17% inversion in 4 hours.

Camphor.—When (+)-camphor was reduced under the conditions used for the other ketones, the reaction was much slower, requiring 9 hours, and small quantities of isopropyl alcohol had to be added at intervals to maintain the volume and keep down the internal temperature. The yield of borneols appeared to be nearly quantitative, but a clean distillation could not be effected.

Exploratory work showed that the mixture could be esterified with *p*-nitrobenzoyl chloride without appreciable decomposition of borneol or isoborneol. Accordingly, the esterification was carried out in benzene solution, with a slight excess of *p*-nitrobenzoyl chloride and pyridine, at room temperature overnight. Working up was done in the usual way, with thorough steam-distillation to remove any traces of camphor or camphene. Yield, nearly quantitative.

The mixture of (+)-bornyl and (–)-isobornyl *p*-nitrobenzoates was assayed by determining the rotation of an 8.3% solution in toluene. A series of closer approximations showed that the solution should contain 2.5% of (+)-bornyl *p*-nitrobenzoate. When the rotation of such a solution was determined it corresponded to that for a mixture with 70% of (–)isobornyl *p*-nitrobenzoate, $[\alpha]_D^{14}$ -15.6° . The reduction of camphor thus yielded 70% of isoborneol.

(–)-4-isoPropylcyclohex-2-en-1-one.—One reduction was done by the modified procedure, in which the ketone (24.5 g.), a_D^{19} -64.7° , in isopropyl alcohol (100 ml.) was added during 4.5 hours. Reduction was complete in a further 1.5 hours. The yield of mixed alcohols was 95%, and the rotation (a_D^{17} -47.4°) agreed with values reported by Gillespie, Macbeth, and Mills (*loc. cit.*) and indicated presence of 39% of *cis*-epimer. Oxidation with potassium dichromate and sulphuric acid regenerated a ketone, a_D^{16} -63.6° (80% yield).

Reductions of Menthone with Higher Alkoxides.

Preparation of Alkoxides.—Aluminium *sec*-butoxide was prepared by the method commonly used for aluminium isopropoxide and was distilled *in vacuo*; b. p. $137^{\circ}/1$ mm. It could not be induced to crystallise (cf. Robinson and Peake, *J. Physical Chem.*, 1935, **39**, 1125) (Found: Al, 11.1. Calc. for $C_{12}H_{27}O_3Al$: Al, 10.9%).

Methylisobutylcarbinol, prepared by pressure hydrogenation of mesityl oxide over Raney nickel at 130 – 150° and subsequent fractional distillation, also dissolved amalgamated aluminium foil readily at the b. p. The product could be distilled *in vacuo*, although it caused troublesome frothing. Aluminium tri-(4-methylpent-2-oxide) was an uncrystallisable syrup, b. p. $203^{\circ}/0.7$ mm., infinitely miscible with methylisobutylcarbinol (Found: Al, 8.3. $C_{18}H_{39}O_3Al$ requires Al, 8.2%).

Methyl-*tert*-butylcarbinol was prepared by pressure hydrogenation of pinacolone over Raney nickel at 130° and was carefully distilled to give a sample with sharp b. p. of 120° . This alcohol dissolved aluminium dusted with mercuric chloride only slowly, the complete reaction requiring 3 days' heating in an oil-bath at 150° . Aluminium tri-(3:3-dimethylbut-2-oxide) was an infusible solid, readily soluble in hot, but sparingly in cold, methyl-*tert*-butylcarbinol and sparingly in cold light petroleum. Small quantities appeared to sublime at $280^{\circ}/0.5$ mm., but larger batches decomposed. The crude alkoxide was dissolved in an equal volume of boiling methyl-*tert*-butylcarbinol, the dark solution was filtered

through Supercel on a sintered-glass plate, and on cooling small off-white crystals (60%) separated, which were washed with cold light petroleum and dried *in vacuo* (Found : Al, 7.8%).

Method of Working.—The same apparatus as before was used, with alterations to permit the use of somewhat reduced pressure, to ensure approximately the same reaction temperature as was used for aluminium isopropoxide. Equalisation of pressure in the dropping funnel allowed easy addition of reagents, and the use of a Perkin triangle permitted periodic testing of the distillate. A stream of dry nitrogen led through a capillary ensured smooth boiling. The use of the long column was necessary for efficient separation of the higher-boiling alcohols from the corresponding ketones, but made it more difficult to keep the reaction temperature sufficiently low towards the end of the reactions.

The usual 2 : 4-dinitrophenylhydrazine reagent was satisfactory for detecting methyl ethyl ketone in the distillate when *sec.*-butyl alcohol was used, but not for detecting the presence of ketones in the other, water-insoluble, alcohols. To detect the presence of methyl isobutyl ketone in methylisobutylcarbinol, a modified reagent was made by saturating 25% acetic acid in water with 2 : 4-dinitrophenylhydrazine and the 2 : 4-dinitrophenylhydrazone of methyl isobutyl ketone. When 0.5 ml. of distillate was added to 3 ml. of this reagent, a homogeneous solution was obtained, which developed a yellow opalescence or turbidity if methyl isobutyl ketone was present. This test was not as sensitive as those for acetone and methyl ethyl ketone. To detect the presence of pinacolone in the distillate from methyl-*tert.*-butylcarbinol, change in b. p. seemed to be the best criterion available.

The same relative proportions of menthone and aluminium alkoxide, and the same concentrations, were used as in the preceding experiments. The higher boiling points of the alcohols did not interfere with working up and distillation of the products in the usual way.

Use of Aluminium sec.-Butoxide.—Reduction required 4 hours, and pressure in the system was held at 360 mm. A 96% yield of menthols was obtained with $\alpha_D^{23} +4.2^\circ$ (homogeneous), which on oxidation gave menthone with $\alpha_D^{18} -18.9^\circ$. These values indicated that the (-)-menthone gave 75% of (+)-*neomenthol* on reduction, and was inverted to (+)-*isomenthone* to the extent of 5.5%.

Use of Aluminium Tri-(4-methylpent-2-oxide).—It was necessary to carry out the reduction at 100 mm. to maintain a reaction temperature of 88°, and even then it rose sharply to 100° near the end of the 5-hour period which was required. The yield was 94%, α_D^{16} was $+1.8^\circ$, and the extent of inversion about 10%, as shown by the rotation, $\alpha_D^{15} -13.7^\circ$, of the derived menthone. The calculated proportion of (+)-*neomenthol* in the reduction of (-)-menthone in this experiment was 72%, but there is some uncertainty in this figure. A duplicate experiment gave the same result.

Use of Aluminium Tri-(3 : 3-dimethylbut-2-oxide).—Reaction was rather slower and, although the temperature at the still-head indicated complete reduction in 5 hours, the reaction was continued for a further 2 hours. Working at a pressure of 200 mm. gave a temperature of 78° at the still-head, but the internal temperature tended to rise to 110°, notwithstanding the addition of more methyl-*tert.*-butylcarbinol at intervals. Menthols were obtained in 94% yield and had $\alpha_D^{23} +10.1^\circ$. Oxidation gave a menthone with $\alpha_D^{21} -11.2^\circ$, indicating about 13% of inversion of (-)-menthone. The percentage of (+)-*neomenthol* formed in the reduction of the (-)-menthone was apparently 86%, but on account of the difficulties encountered in the reduction this figure may not be strictly comparable with those from the other reductions.

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